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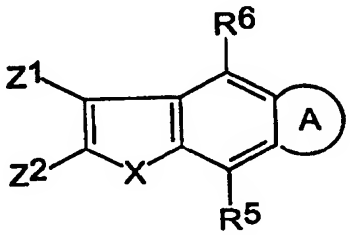


(1)

(57) Abstract

The present invention relates to use of a compound of formula (1) as an immunomodulatory or anti-inflammatory drug or for use in the treatment of a therapeutic indication in which inhibition of dehydro-orate dehydrogenase (DHODH) is beneficial and salts and physiologically functional salts thereof, wherein X, $R^5$, $R^6$, A, $Z^1$ and $Z^2$ have the meanings given in Claim 1.

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# CONDENSED HETEROCYCLIC COMPOUNDS AS ANTI-INFLAMMATORY AND IMMUNOMODULATORY AGENTS

The present invention relates to the use of various heterocyclic compounds as immunomodulatory or anti-inflammatory drugs, or in the treatment of therapeutic indications relating to inhibition of dehydro-orate dehydrogenase. More specifically, the present invention relates to the use of Pyrrolo [3,2-*b*] carbazoles, Pyrrolo [2,3-*b*] carbazoles, 1H- Benzofuro [2,3-*f*] indoles, 1H-Benzofuro [3,2-*f*] indoles, 1H-[1] Benzothieno [2,3-*f*] indoles, 1H-[1] Benzothieno [3,2-*f*] indoles, benzo[1,2-b:4,5-b']dipyrroles, benzo[2-b:5,4-b']dipyrroles, cyclopent[f]indoles, benzo[1,2-b:4,5-b']difurans, benzo(1,2-b:5,4-b']difurans, 2H-indeno[5,6-b]furans, benzo[1,2-b:4,5-b']dithiophenes, benzo[1,2-b:5,4-b']dithiophenes, cyclopent[f] indenes and 5H-furo[ 2,3-f]indoles for the aforementioned purposes.

The aforementioned heterocyclic compounds have been described in published International Patent Applications Nos WO94/02483, WO95/21170, WO95/21171 and WO96/01827, which also disclose anti tumour activity for the compounds.

Khoshtariya et al disclose the synthesis of certain indolobenzo[b] thiophenes and certain indolobenzo[b] furans, khim. Geterotsikl. Soedin (1980), (2) 203-8, and khim Geterotsiki Soedin (1984), (10)1366-70 respectively.

Kakhabrishvili et al, khim Geterotsikl Soedin (1985), (3) 355-8 disclose the synthesis of certain derivatives of indolo[5,6-*d*] and indolo [5,4-*d*] benzo[b] furans.

EP447,703 discloses the synthesis of certain benzo[5,6-*b*]benzofuran-2-carboxylates.

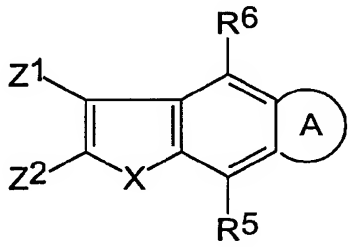
L.Chunchatprasert et al, J.Chem.Soc., Perkin Trans I, 1779 (1992) disclose the synthesis of pyrrolo[3,2-b]carbazoles, 1H-benzofuro[3,2-*f*]indoles and 1H-[1] benzothieno[2,3-*f*]indoles.

Gruenhaus H., J. Heterocyclic Chem., 13(6) 1161-3 discloses the synthesis of certain indenothiophenes.

It has now been found that the compounds employed in the present invention are inhibitors of dehydro-orate dehydrogenase (DHODH), and are useful as

immunosuppressive and anti-inflammatory drugs and in the treatment of therapeutic indications in which inhibition of DHODH is beneficial.

According to the present invention there is provided use of a compound of formula (1) in the manufacture of a medicament for use as an immunomodulatory or anti-inflammatory drug or for use in the treatment of a therapeutic indication in which inhibition of dehydro-orate dehydrogenase (DHODH) is beneficial:-



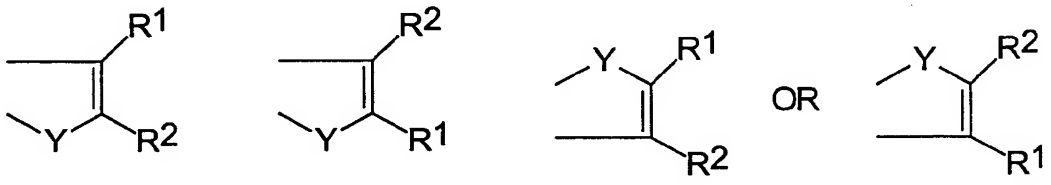
(1)

and salts and physiologically functional salts thereof,

wherein X is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$, wherein $R^7$ is H or the following groups which may be optionally substituted: cyloalkyl, cycloalkenyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, acyl, aroyl, sulphonyl, alkylsulphonyl, arylsulphonyl or COOR;

$R^5$ and $R^6$ are independently selected from H, hydroxy, nitro, amino, halo, cyano, CHO, $COR^8$, $CO_2R^8$ and the following groups which may be optionally substituted: alkyl, aryl, aryloxy, aralkyloxy, alkoxy, aralkyl, wherein $R^8$ is optionally substituted alkyl and aryl;

A is:




wherein $R^1$ is $COR^8$, CHO, $CH_2OH$, $CH_2OR^8$, $CONH_2$, $COOR^8$, $CONHR^8$, $CONR^8R^8$, $CONHNR^8R^8$, $COO(CH_2)_nNR^8R^8$, $CSOR^8$, $CSSR^8$, $COSR^8$, $CSNHR^8$, $CSNR^8$ $R^8$,

$CNHOR^8$ or an optionally substituted 5 or 6 membered aromatic or nonaromatic heterocyclic ring containing 1 to 4 heteroatoms,

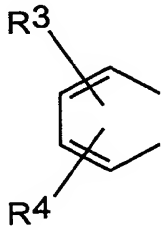
wherein the groups $R^8$ are independently selected from hydrogen, optionally substituted alkyl, aryl, aralkyl, acyl, alkoxyalkyl, heterocycloalkyl and heteroaralkyl groups, and $C_{1-10}$ optionally substituted hydrocarbyl groups which may contain one or two oxygen atoms in the chain and wherein n is 1 to 4;

or $R^8$ may independently be sugar groups;

$R^2$ is H, hydroxy, haloalkyl, halo, cyano, $COOR^8$, alkyl, aryl, alkenyl, alkynyl, alkoxy, (wherein alkyl, aryl, alkenyl, alkynyl and alkoxy can be substituted) $CH_2CH_2CO_2R^9$ (wherein $R^9$ is alkyl or aryl), CHO, $COR^8$, $COOR^8$ or a $C_{1-10}$ optionally substituted hydrocarbyl group which may contain one or two oxygen atoms in the chain, wherein $R^8$ is independently selected from the groups defined for $R^8$ above;

Y is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$ wherein $R^7$ is independently selected from groups hereinbefore defined for $R^7$;

$Z^1$ and $Z^2$ are independently selected from H, halogen, cyano, amino, alkyl, $COOR^8$, $CONHR^8$, $COR^8$, $CH_2OH$, $CH_2OR^8$, $CONH_2$, CON $R^8R^8$, $CSOR^8$, $CSSR^8$, $COSR^8$, $CSNHR^8$, $CSNR^8R^8$ and $CNHOR^8$ wherein $R^8$ is independently selected from the groups defined for $R^8$ above; or $Z^1$ and $Z^2$ together form the group:




wherein $R^3$ and $R^4$ are independently selected from H, hydroxy, alkyl, haloalkyl, alkoxy, halo, cyano, azido, nitro, amino, alkyl amino, dialkyl amino, CHO, $COR^8$, $CONHR^8$, CON $R^8R^8$ (wherein $R^8$ is independently selected from the groups defined for $R^8$ above ),carboxyl or $CO_2R^{10}$, wherein $R^{10}$ is independently selected from alkyl, aralkyl and aryl.

The term hydrocarbyl includes straight-chain or branched alkyl, alkenyl and alkynyl groups; cycloalkyl, cycloalkenyl and cycloalkynyl groups; and aralkyl, aralkenyl and aralkynyl groups where the alkyl, alkenyl or alkynyl portion may be straight-chain or branched.

Alkyl groups may be straight or branched chain alkyl groups, and may contain 1-10 carbon atoms and suitably 1-6 carbon atoms. Examples of such alkyl groups include methyl, ethyl, t-butyl and the like.

Alkenyl groups may be straight or branched chain alkenyl groups, and may contain 2-10 carbon atoms and suitably 2-6 carbon atoms. Examples of such alkenyl groups include ethenyl, butenyl and the like.

Alkynyl groups may be straight or branched chain alkynyl groups, and may contain 2-10 carbon atoms and suitably 2-6 carbon atoms. Examples of such alkynyl groups include ethynyl, propynyl and the like.

Haloalkyl groups may be straight or branched chain haloalkyl groups and may contain 1-10 carbon atoms and suitably 1-6 carbon atoms. Such groups may contain one or more halo atoms. Examples of haloalkyl groups include trifluoromethyl, and the like.

Acyl groups are derived from carboxylic acids and may be straight or branched and may contain 1-10 carbon atoms and suitably 1-6 carbon atoms. Examples of suitable acyl groups include ethanoyl and propanoyl groups.

Alkoxy may be straight or branched and may contain 1-10 carbon atoms and suitably 1-6 carbon atoms. Examples of suitable alkoxy groups include methoxy, ethoxy and the like.

Aryl includes both carbocyclic aryl groups and heterocyclic aryl groups normally containing a maximum of 10 ring atoms. Carbocyclic aryl groups include, eg phenyl and naphthyl and contain at least one aromatic ring. Heterocyclic aryl groups include eg thienyl, Riryl, pyridyl, indolyl and quinolinyl rings.

An aralkyl group may contain from 1 to 4 atoms in the alkyl portion and the aryl portion may be a carbocyclic or heterocyclic aryl group.

A $C_{1-10}$ hydrocarbyl group optionally containing one or two oxygen atoms includes

alkyl, hydroxyalkyl, alkenyl, alkynyl, $C_{1-10}$ carbamoylalkyl, $C_{1-10}$ alkoxyalkyl, cycloalkyl, cycloalkenyl, aralkyl, $C_{1-10}$ aryloxyalkyl, acyl or aryl.

Hydrocarbyl, aryl, alkyl, alkenyl, alkynyl and aralkyl groups may be optionally substituted by hydroxy, azido, alkenyl, halo, nitro, amino (optionally substituted by one or 2 alkyl groups), cyano, carboxylate, alkyl ester, aralkyl ester, aryl ester (wherein the alkyl ester, aralkyl ester and aryl ester can be substituted) alkyl, aryl, aralkyl, aryloxy, arylalkoxy, substituted arylalkoxy, sulphinyl, sulphonyl, thio, $C_{1-10}$ alkylthio, alkoxy, hydroxyalkyl, haloalkyl, phosphate, phosphonate, silyl, silyloxy, (wherein silyl and silyloxy may be substituted by one or more $C_{1-6}$ alkyl or aryl groups) keto or, formyl.

Cycloalkyl includes both cycloalkyl groups and heterocycloalkyl groups normally containing between 3 and 6 ring atoms. Heterocycloalkyl groups include e.g. morpholino, thiomorpholino, piperidino, imidazolino, imidazolidino, pyrrolidino, pyrazolidino, piperazino, tetrahydrofuranyl, tetrahydropyranyl. Cycloalkyl groups include $C_{3-6}$ carbocycles such as cyclopentyl and cyclohexyl.

Cycloalkenyl includes both cycloalkenyl groups and heterocycloalkenyl groups normally containing between 3 and 6 ring atoms.

Substituents which may be present on alkyl esters, aralkyl esters and aryl esters include nitro, amino, hydroxy, alkoxy, halogen, cyano or alkyl.

Examples of suitable aromatic 5- or 6-membered rings containing 1 to 4 heteroatoms, include oxadiazole, oxazole, isoxazole, imidazole, pyrazole, triazole, tetrazole, pyrimidine, pyrazine, pyridazine, triazine, thiadiazole, thiazole, isothiazole.

Examples of suitable non-aromatic 5- or 6- membered rings containing 1 to 4 heteroatoms, include oxazoline, oxazolidine, thiazoline, thiazolidine, oxazolidinone, thiazolidinone, imidazoline, imidazolidine, pyrazolidine and pyrazoline.

Substituents which may be present on $R^1$ include azido, nitro, cyano, halo, haloalkyl, hydroxy, CHO, $COR^8$ , $CO_2R^8$, $CONHR^8$, $CONR^8R^8$, oxo or the following groups which may be optionally substituted: alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, aralkyl, heteroaryl, acyl, aroyl, aralkoyl, alkoxy or amino.

Substituents which may be present on cycloalkyl, cycloalkenyl, alkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl, acyl, aroyl, alkylsulphonyl or arylsulphonyl groups include alkyl, alkoxy, halo, sulphinyl, hydroxy, amino (optionally substituted by one or

two alkyl groups or part of a heterocyclic ring), haloalkyl (eg trifluoromethyl), sulphonyl, cyano, nitro or azido.

Substituents which may be present on the sulphonyl and sulphinyl include alkyl, aryl and aralkyl.

Halo represents fluoro, chloro, bromo or iodo.

Where $R^8$ is a sugar this group may be present in a protected or unprotected form. Preferred sugar-protecting groups include isopropylidene, benzylidene acetate, benzoyl, paranitrobenzyl, paranitrobenzoyl, benzyl, substituted silyl and tetrahydropyranyl.

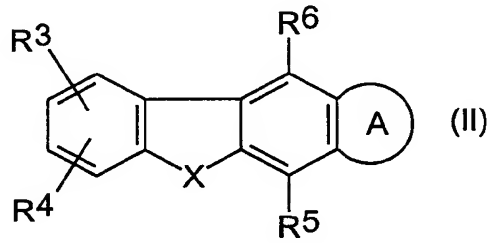
When $R^8$ is a sugar such as a tetrose, pentose, hexose (including furanose and pyranose) or heptose, preferred sugars include glucose, fructose, mannose, ribose, arabinose.

X preferably represents S, O or NH; more preferably S or NH; more preferably NH.

$R^5$ and $R^6$ are preferably independently selected from H, alkyl and aryl; more preferably from H and alkyl.

Y preferably represents NH.

In a first series of preferred compounds there is provided a compound of the general formula (II)




(II)

and salts and physiologically functional derivatives thereof,

wherein A is as hereinbefore defined,

X is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$, wherein $R^7$ is H, alkyl, aralkyl, aryl, alkenyl, acyl, alkynyl, sulphonyl or substituted sulphonyl;

Y is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$;

$R^1$ is $COR^{11}$, $COOR^{11}$, CHO, $CH_2OH$, $CH_2OR^{12}$, $CONH_2$, $CONHR^{13}R^{14}$, $CONHR^{13}$, $CONR^{13}R^{14}$, $COO(CH_2)_nNR^{13}R^{14}$, wherein $R^{11}$ is H, alkyl, aryl, substituted aryl or aralkyl, $R^{12}$ is acyl or substituted acyl, $R^{13}$ and $R^{14}$ are independently hydrogen, alkyl or aryl, and n is 1 to 4 carbon atoms;

$R^2$ is H, $COOR^{11}$, alkyl, aryl, substituted aryl or $CH_2CH_2CO_2R^9$ wherein $R^9$ is alkyl or aryl;

$R^3$ and $R^4$ are independently H,hydroxy, alkyl, haloalkyl, alkoxy, halo, cyano, nitro, amino, alkyl amino, dialkyl amino, substituted alkyl, carboxyl or $CO_2R^9$;

$R^5$ is H, alkyl, substituted alkyl, aralkyl, nitro, amino, halo, cyano, CHO, $COOR^{11}$;

$R^6$ is H, aryl, alkyl, aralkyl, nitro, halogen, CHO or $COR^{15}$ wherein $R^{15}$ is alkyl or aryl.

In the first series of preferred compounds, it is further preferred that:-

X is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$ , wherein $R^7$ is H, alkyl, aralkyl, aryl, alkenyl, acyl, alkynyl or sulphonyl;

Y is O, S, SO, $SO_2$,$CH_2$, CO or $NR^7$ ;

$R^1$ is $COOR^{11}$,CHO,$CH_2OH$, $CH_2OR^{12}$, $CONH_2$ , $CONHR^{13}$ or $CONR^{13}R^{14}$, wherein $R^{11}$ is H, alkyl, aryl, substituted aryl or aralkyl, $R^{12}$ is acyl or substituted acyl, and R and R are independently alkyl or aryl;

$R^2$ is H, $COOR^{11}$, alkyl, aryl, substituted aryl or $CH_2CH_2CO_2R^9$ wherein $R^9$ is alkyl or aryl;

$R^3$ and $R^4$ are independently H, hydroxy, alkyl, haloalkyl, alkoxy, halo, cyano, nitro,

amino, alkyl amino, dialkyl amino, substituted alkyl, carboxyl or $CO_2R^9$;

$R^5$ is H, alkyl, substituted alkyl, aralkyl, nitro, halo, cyano, CHO;

$R^6$ is H, alkyl, aralkyl, nitro, halo, CHO or $COR^{15}$
wherein $R^{15}$ is alkyl or aryl;

X is preferably O, S or $NR^7$, wherein $R^7$ is H, alkyl, sulphonyl or toluene sulphonyl;

Y is preferably $NR^7$;

$R^1$ is preferably $COR^{11}$ , $COOR^{11}$ , $CH_2OR^{12}$, $CONH_2$, $CNHNR^{13}R^{14}$, $CONHR^{13}$, $CONR^{13}R^{14}$, $COO(CH_2)_n NR^{13}R^{14}$, wherein $R^{11}$ is H, alkyl, aryl, substituted aryl or aralkyl, $R^{12}$ is acyl or substituted acyl, and $R^{13}$and $R^{14}$ are independently hydrogen, alkyl or aryl and n is 1 to 4 carbon atoms;

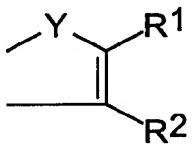
$R^2$ is preferably $COOR^{11}$, alkyl or $CH_2CH_2CO_2R^9$ wherein $R^9$ is alkyl or aryl;

$R^3$ and $R^4$ represent independently H,hydroxy, alkyl, alkoxy, halogen, cyano, substituted alkyl or carboxyl;

$R^5$ is preferably H or alkyl;

$R^6$ is preferably H, alkyl or aryl and salts.

X preferably represents S or NH, A is preferably




and Y preferably represents NH.

$R^1$ is preferably $COOR^{11}$, with $R^{11}$ preferably being alkyl or aralkyl.

$R^2$ is preferably H or alkyl.

$R^3$ is preferably H, alkoxy or halo.

$R^4$ is preferably H, alkoxy or halo.

$R^5$ is preferably alkyl and

$R^6$ is preferably H

Particularly preferred compounds include:

3-Pyridyl 3, 4-dimethylpyrrolo( 3, 2-b] carbazole-2-carboxylate
[(3-Dimethylamino)phenyl]3, 4-dimethylpyrrolo[3,2-b] carbazole-2-carboxylate
Benzyl 1, 3, 4- trimethylpyrrolo( 3, 2-b] carbazole-2-carboxylate
Phenyl 3, 4-dimethylpyrrolo[ 3, 2-b] carbazole-2-carboxylate
3,4-Dimethyl-2-( 1-imidazolylcarbonyl ) pyrrolo [3, 2-b] carbazole
Ethyl 3, 4-dimethylpyrrolo [3,2,-b]carbazole-2-carboxylate;
Ethyl 3, 4-dimethylbenzothieno [4, 5-f] indole-2-carboxylate;
Benzyl 3, 4-dimethylpyrrolo [3, 2-b] carbazole-2-carboxylate;
Benzyl 8-f luoro-3, 4-dimethylpyrrolo [3,2-b] carbazole-2-carboxylate;
Ethyl 8-f luoro-3, 4-dimethylpyrrolo [3,2-b] carbazole-2-carboxylate
Benzyl 3,4, 6-trimethylpyrrolo (3, 2-b] carbazole-2-carboxylate;
Ethyl 3,4, 6-trimethylpyrrolo [3, 2-b] carbazole-2-carboxylate;
8-Fluoro-3, 4-dimethylpyrrolo[ 3, 2-b] carbazole-2-carboxylic acid
3,4-Dimethylpyrrolo[ 3, 2-_b] carbazole-2-carboxylic acid;
Ethyl 8-methoxy-3,4-dimethylpyrrolo [3, 2-b] carbazole-2-carboxylate;
3,4,6-Trimethylpyrrolo [3, 2-b] carbazole-2-carboxylic acid and
Benzyl 8-methoxy-3, 4-dimethylpyrrolo [3, 2-_b] carbazole-2-carboxylate;

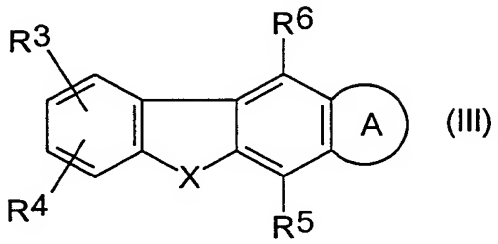
and physiologically functional derivatives thereof.

Especially preferred is Ethyl 3, 4-dimethylpyrrolo [3,2,-b]carbazole-2-carboxylate and physiologically functional derivatives thereof.

Compounds in the first series may be prepared according to the reaction schemes and procedures described in published International Patent Application No. WO94/02483,

incorporated herein by reference.

A second series of preferred compounds have the formula (III)




(III)

and salts and physiologically functional derivatives thereof,
wherein A is as hereinbefore defined,

X is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$, wherein $R^7$ is H, alkyl, aralkyl, aryl, alkenyl, acyl, alkynyl, sulphonyl or substituted sulphonyl;

Y is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$;

$R^1$ is $COOR^{16}$, $CONHR^{16}$, $CONR^{16}R^{17}$, $CSOR^{16}$, $CSSR^{16}$, $COSR^{16}$, $CSNHR^{16}$, $CSNR^{16}R^{17}$, $CNHOR^{16}$ wherein $R^{16}$ and $R^{17}$ are independently $C_{1-10}$ optionally substituted hydrocarbyl groups which may optionally contain one or two oxygen atoms in the chain; or $R^{16}$ and $R^{17}$ are independently alkoxyalkyl, heterocycloalkyl, heteroaralkyl,

or $R^{16}$ and $R^{17}$ may independently be sugar groups;

$R^2$ is H, halo, cyano, $COOR^{16}$, alkyl, aryl, alkenyl, alkynyl, alkoxy, (wherein alkyl, aryl, alkenyl, alkynyl and alkoxy can be substituted) or $CH_2CH_2CO_2R^9$ wherein $R^9$ is alkyl or aryl;

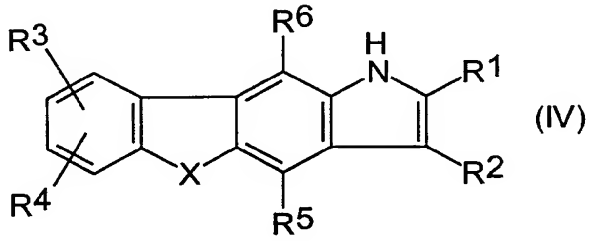
$R^3$ and $R^4$ are independently H,hydroxy, alkyl, haloalkyl, alkoxy, halo, cyano, nitro,

amino, alkyl amino, dialkyl amino, substituted alkyl, carboxyl or $CO_2R^9$;

$R^5$ is H, hydroxy, aryloxy, aralkyloxy, alkyl, substituted alkyl, aralkyl, nitro, amino, halo, cyano, CHO; and

$R^6$ is H, aryl, alkyl, aralkyl, nitro, halogen, CHO or $COR^{15}$ wherein $R^{15}$ is alkyl or aryl.

Particularly preferred compounds in the second series have the formula (IV)




(IV)

wherein,
X preferably represents S,O or NH;

$R^1$ is preferably $COOR^{16}$, with $R^{16}$ preferably being a group of formula

$$-(CH_2COO)_n Z$$

where n is 0 or 1 and
Z is a phenyl or benzyl group optionally substituted by one or more groups selected from hydroxy, carboxyl, nitro, amino, phthalimido, p-nitrobenzyl and p-nitrobenzyloxy;

or Z is a $C_{1-4}$ straight or branched alkyl or cycloalkyl group optionally substituted by one or more groups selected from hydroxy, carboxyl, halo, amino, dialkylamino, alkylsulphinyl, alkylsulphonyl and benzyloxy;

or Z is a substituted glucofuranosyl moiety;

$R^2$ is preferably H or alkyl;

$R^3$ is preferably H, alkoxy, hydroxy or halo;

$R^4$ is preferably H, alkoxy, hydroxy or halo;

$R^5$ is preferably alkyl; and

$R^6$ is preferably H.

and salts and physiologically functional derivatives thereof.

Particularly preferred compounds include:

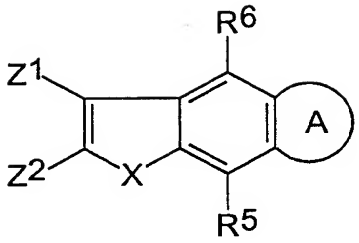
[(2-Dimethylamino)ethyl] 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(2-Methylsulphonylethyl) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(2-Methylsulphinylethyl) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(1,3-Dibenzyloxypropyl-2) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(1-Benzyloxy-3-hydroxypropyl-2) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(1,3-Dihydroxypropyl-2) 3,4-dimethyl-pyrrolo[3,2-b]carbazole-2-carboxylate
(2-Amino-2-methylpropyl-1) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(4-Nitrophenylmethyl) 2-(3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxy)acetate
2-(3,4-Dimethylpyrrolo[3,2-b]carbazole-2-carboxy)acetic acid
Cyclohexyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
Cyclohexylmethyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
Cyclopentyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
Cyclooctyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
3,5-Di(tert-butyldiphenylsilyloxy)cyclohexyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
3,5-Dihydroxycyclohexyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
cis-4-tert-Butyldiphenylsilyloxycyclohexyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
cis-4-Hydroxycyclohexyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
trans-4-tert-Butyldiphenylsilyloxycyclohexyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
trans4-Hydroxycyclohexyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
Tetrahydro-2H-pyran4-yl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
1-Benzylpiperidin-4-yl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
Piperidin-4-yl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
1-Methylpiperidin-4-yl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(3,4-Dimethylpyrrolo[3,2-b]2-carbazolyl)3-O-( 1,2:5,6-di-O-isopropylidene

glucofuranoside)
(3,4-Dimethylpyrrolo[3,2-b]2-carbazolyl) 3-O-(1,2-O-isopropyl-ideneglucofuranoside)
[3-(4-Nitrophenylmethoxy)phenyl] 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(3-Hydroxyphenyl) 3-4,-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(4-Phthalamidophenyl) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
4-(Aminophenyl) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(4-Nitrophenylmethyl) 3-(3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxy)benzoate
3-(3,4-Dimethylpyrrolo[3,2-b]carbazole-2-carboxy)benzoic acid
3-(tert-Butyldiphenylsilyloxymethyl)phenyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(3-Hydroxymethyl)phenyl 3 ,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
[3-(4-Nitrophenylmethoxy)phenyl] 4-methyl-1H-[1]benzothieno[2,3 –f]indole-2-carboxylate
(3-Hydroxyphenyl)4-methyl 1H-[1]benzothieno[2,3-f]indole-2-carboxylate
3-(4-Nitrophenylmethoxy)phenylmethyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
3-(tert-Butyldiphenylsilyloxyphenyl)methyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(3-Hydroxyphenyl)methyl 3 ,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(1-Hydroxy-3-methylpropyl-2) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxamide
2-Hydroxyethyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxamide
2-Chloroethyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxamide
N-(2-Aminoethyl) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxamide
N-(2-Acetamidoethyl) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxamide
(3-Aminopropyl- 1) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxamide
2-Hydroxyethyl 4-methyl- 1H-[1]benzothieno[2,3-f]indole-2-carboxamide
2-Chloroethyl 4-methyl-1H-[l]benzothieno[2,3-f]indole-2-carboxamide

and physiologially functional derivatives thereof.

Compounds in the second series may be prepared according to the reaction schemes and procedures described in published International Patent Application No. WO95/21170, incorporated herein by reference.

In a third series of preferred compounds there is provided a compound of the general formula (V)




(V)

or a salt or physiologically functional derivative thereof,
wherein A is as hereinbefore defined

X is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$, wherein $R^7$ is H, alkyl, aralkyl, aryl, alkenyl, acyl, alkynyl, sulphonyl, substituted sulphonyl, or COOMe;

Y is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$;

$R^1$ is $COR^{18}$, CHO, $CH_2OH$, $CH_2OR^{18}$, $CONH_2$, $COOR^{18}$, $CONHR^{18}$, $CONR^{18}R^{19}$, $CSOR^{18}$, $CSSR^{18}$, $COSR^{18}$, $CSNHR^{18}$, $CSNR^{18}R^{19}$, $CNHOR^{18}$ wherein $R^{18}$ and $R^{19}$ are independently hydrogen, alkoxyalkyl, heterocycloalkyl, heteroaralkyl, or $C_{1-10}$ optionally substituted hydrocarbyl group which may optionally contain one or two oxygen atoms in the chain;

or $R^{18}$ and $R^{19}$ may independently be sugar groups;

$R^2$ is H, halo, cyano, $COOR^{18}$, alkyl, aryl, alkenyl, alkynyl, alkoxy, (wherein alkyl, aryl, alkenyl, alkynyl and alkoxy can be substituted) or $CH_2CH_2CO_2R^9$ wherein $R^9$ is alkyl or aryl;

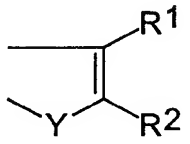
$Z^1$ is H, alkyl, halogen, cyano, amino, $COOR^{18}$, $CONHR^{18}$, $COR^{18}$, $CH_2OH$, $CH2OR^{18}$, $CONH_2$, $CONR^{18}R^{19}$, $CSOR^{18}$, $CSSR^{18}$, $COSR^{18}$, $CSNHR^{18}$, $CSNR^{18}R^{19}$ or $CNHOR^{18}$;
$Z^2$ is H, halogen, cyano, amino, alkyl, $COOR^{18}$, $CONHR^{18}$, $COR^{18}$, $CH_2OH$, $CH_2OR^{18}$, $CONH_2$, $CONR^{18}R^{19}$, $CSOR^{18}$, $CSSR^{18}$, $COSR^{18}$, $CSNHR^{18}$, $CSNR^{18}R^{19}$ or $CNHOR^{18}$;

$R^5$ is H, hydroxy, aryloxy, aralkyloxy, alkyl, substituted alkyl, aralkyl, nitro, amino,

halo, cyano, $COOR^{18}$ or CHO;

$R^6$ is H, aryl, alkyl, aralkyl, nitro, halogen, CHO or $COR^{20}$ wherein $R^{20}$ is alkyl or aryl.

X preferably represents NH, A is preferably




and Y preferably represents NH.

$R^1$ is preferably $COOR^{18}$, with $R^{18}$ preferably being alkyl or aralkyl.

$R^2$ is preferably H, alkyl, or $COOR^{18}$ wherein $R^{18}$ is preferably alkyl,

$Z^1$ is preferably alkyl

$Z^2$ is preferably alkyl or $COOR^{18}$.

$R^5$ is preferably hydrogen and

$R^6$ is preferably hydrogen or methyl.

Preferred groups of compounds include:

Ethyl 1,7-dihydro-3,4,6-trimethylpyrrolo[3,2-f]indole-2-carboxylate;
Diethyl 1,7-dihydro-3,4,6-trimethylpyrrolo[3,2-f] indole-2,5-dicarboxylate; and
Ethyl 6-methoxycarbonyl-3,4-dimethylpyrrolo [3,2-f]indole-2-carboxylate

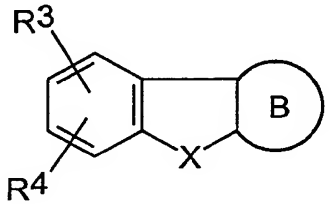
and physiologically functional derivatives thereof; and

Ethyl 6-Benzyloxycarbonyl-3,4-dimethylpyrrolo[3,2-f ]indole-2-carboxylate;
Dibenzyl 3,4-dimethylpyrrolo[3,2-f]indole-2,6-dicarboxylate;

Ethyl 7-methoxycarbonyl-3,4-dimethylpyrrolo [3,2-f]indole-2-carboxylate; and
Ethyl 3,4-dimethylpyrrolo[3,2-f]indole-2-carboxylate
and physiologically functional derivatives thereof.

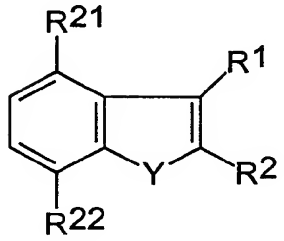
Compounds in this third series may be prepared according to the reaction schemes and procedures described in published International Patent Application No. WO95/21171.

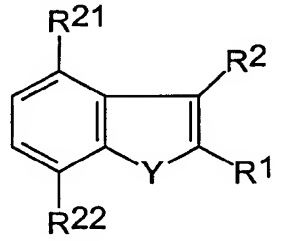
In a fourth series of preferred compounds there is provided a compound of the general formula (VI)




(VI)

and salts and physiologically functional derivative thereof,
wherein B is

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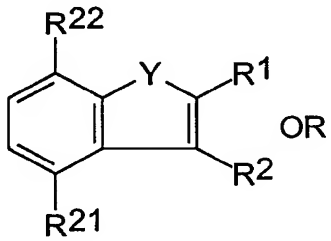
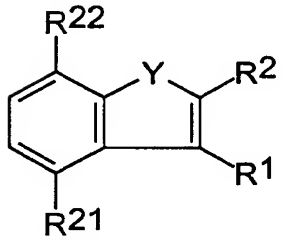



X is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$, wherein $R^7$ is H or the following groups which may be optionally substituted: cyloalkyl, cycloalkenyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, acyl, aroyl, alkylsulphonyl or arylsulphonyl;

Y is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$;

$R^1$ is an optionally substituted 5- or 6-membered heterocyclic ring containing 1 to 4 heteroatoms wherein the 5- or 6- membered ring may be aromatic or non-aromatic;

$R^2$ is H, hydroxy, halo, haloalkyl, cyano, alkyl, aryl, alkenyl, alkynyl, alkoxy, (wherein alkyl, aryl, alkenyl, alkynyl, and alkoxy can be substituted), CHO, $COR^{23}$, $COOR^{23}$ wherein $R^{23}$ is hydrogen or is a $C_{1-10}$ optionally substituted hydrocarbyl group which may contain one or two oxygen atoms;

$R^3$ and $R^4$ are independently H, hydroxy, alkyl, haloalkyl, azido, CHO, $COR^{23}$, $CO_2R^{23}$, $CONHR^{23}$, $CONR^{23}R^{24}$, alkoxy, halo, cyano, nitro, amino, alkyl amino, dialkyl amino, carboxyl wherein $R^{24}$ is alkyl, aryl or aralkyl;

$R^{21}$ is H, hydroxy, nitro, amino, halo, cyano, CHO, $COR^{23}$, or the following groups which may be optionally substituted: alkyl, aryl, aryloxy, aralkyloxy, alkoxy, aralkyl;

$R^{22}$ is H, hydroxy, amino, nitro, halo, CHO, $COR^{25}$, $CO_2R^{25}$ wherein $R^{25}$ is optionally substituted alkyl or aryl, or $R^6$ is alkyl, aralkyl, or aryl wherein alkyl, aralkyl or aryl may be optionally substituted.

Suitably X is O,S, SO, $SO_2$,$CH_2$,CO or $NR^7$ wherein $R^7$ is suitably H, alkyl, aralkyl, aryl, alkenyl, acyl, alkynyl or optionally substituted sulphonyl;

Suitably $R^1$ is an optionally substituted five or six-membered heterocyclic ring containing one or two nitrogen atoms and optionally one other heteroatom.

Suitably $R^2$ is H, alkyl or $COOR^{23}$ wherein $R^{23}$ is as defined above;

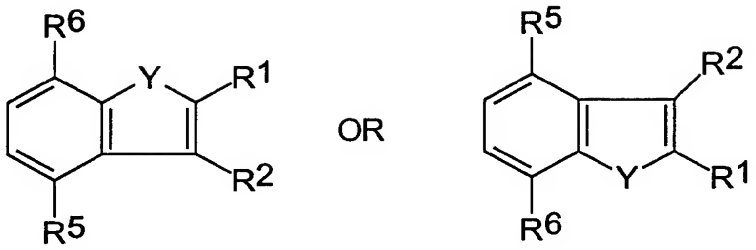
Suitably $R^3$ and $R^4$ are independently H, hydroxy, alkyl, haloalkyl, alkoxy, halo, cyano, nitro, amino, alkylamino, dialkylamino or substituted alkyl;

Suitably $R^{21}$ is H, alkyl, substituted alkyl, aryl, aralkyl, nitro, halo, cyano or CHO;

Suitably $R^{22}$ is H, alkyl, aralkyl, nitro, halo, CHO or $COR^{25}$wherein $R^{25}$ is suitably alkyl or aryl.

X preferably represents S or NH,

B is preferably




and Y preferably represents NH.

$R^1$ is preferably an optionally subsituted five-membered ring containing two nitrogen atoms and one oxygen atom wherein the 5-membered ring may be aromatic or non-aromatic. Preferred substituents are alkyl, aryl or aralkyl;

$R^2$ is preferably H or $C_{1-4}$ alkyl;

$R^3$ is preferably H, alkoxy, halo or hydroxy;

$R^4$ is preferably H, alkoxy, halo or hydroxy;

$R^5$ is preferably H or alkyl; and

$R^6$ is preferably H or alkyl.

Particularly preferred compounds include:

3,4-Dimethyl-2-(3-ethyl-1,2,4-oxadiazol-5-yl) pyrrolo[3,2-*b*]carbazole;
2-(3-Benzyl- 1,2,4-oxadiazol-5-yl)-3,4-dimethylpyrrolo[3,2-*b*]carbazole;
3,4-Dimethyl-2-(3-ethyl-1,2,4-oxadiazol-5-yl) pyrrolo[2,3-*b*]carbazole;
2-(3-ethyl-1,2,4-oxadiazol-5-yl)-4-methyl-1*H*-[1]benzothieno[2,3-*f*]indole;
3,4-Dimethyl-2-(2-methyl-1,3,4-oxadiazol-5-yl)-pyrrolo[3,2-*b*]carbazole;
3,4-Dimethyl-2-(2-ethyl-1,3,4-oxadiazol-5-yl)-pyrrolo[3,2-*b*]carbazole;
3,4-Dimethyl-2-(2-phenyl-1,3,4-oxadiazol-5-yl)-pyrrolo[3,2-*b*]carbazole;
2-(2-Ethyl-1,3,4-oxadiazol-5-yl)4-methyl-1*H*-[1]benzothieno[2,3-*f*]indole;
3,4-Dimethyl-2-[3-(3,4-methylenedioxyphenyl)-1,2,4-oxadiazol-5-yl]pyrrolo[3,2-*b*]carbazole;
4-Methyl-2-(2-oxazolin-2-yl)-1H-[1]benzothieno[2,3-*f*]indole
3,4-Dimethyl-2-(3-methyl-1,2,4-oxadiazol-5-yl)pyrrolo[3,2-*b*]carbazole

3,4-Dimethyl-2-(3-methyl-1,2,4-oxadiazol-5-yl)pyrrolo[2,3-*b*]carbazole
3,4-Dimethyl-2-[(3-phenyl)-1,2,4-oxadiazol-5-yl]pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-(2-oxazolin-2-yl)pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-[3-(1-piperidinylmethyl)-1,2,4-oxadiazol-5-yl)pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-[3-(4-pyridyl)-1,2,4-oxadiazol-5-yl]pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-(3-methoxymethyl-1,2,4-oxadiazol-5-yl)pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-[3-(2-hydroxyethyl)-1,2,4-oxadiazol-5-yl]pyrrolo[3,2-*b*]carbazole
2-(3-Ethyl- 1,2,4-oxadiazol-5-yl)4--methyl- 1*H*-[1]benzofuro[2,3-*f*]indole
3,4-Dimethyl-2-(4,4-dimethyl-2-oxazolin-2-yl)pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-[3-(3-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-[3-(N,N-dimethylaminomethyl)-1,2,4-oxadiazol-5-yl]pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-(tetrazol-5-yl)pyrrolo[3 ,2-b]carbazole)
3,4-Dimethyl-2-[3-(4-morpholinomethyl)-1,2,4-oxadiazol-5-yl)pyrrolo[3,2-b]carbazole
3,4-Dimethyl-2-(3-methoxyethyl- 1,2,4-oxadiazol-5-yl)pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-(1,2,4-oxadiazol-5-yl)pyrrolo[3,2-*b*]carbazole

and salts and physiologically functional derivatives thereof.

Compounds in this fourth series may be prepared according to the reaction schemes and procedures described in published International Patent Application No. WO96/01827, incorporated herein by reference.

According to a further aspect of the present invention there is provided use of a compound of formula (1) as hereinbefore defined in the manufacture of a medicament for use as a DHODH inhibitor.

According to a further aspect of the present invention there is provided a method of treating a patient requiring immunomodulation comprising administering to said patient an effective dose of a compound of formula (1) as defined above.

As used herein immunomodulation may comprise immunopotentiation or immunosuppression, preferably immunosuppression

According to a further aspect of the present invention there is provided a method of treating a patient requiring anti-inflammatory treatment comprising administering to

said patient an effective dose of a compound of formula (1) as defined above.

According to a further aspect of the present invention there is provided a method of treating a patient having a condition in which inhibition of DHODH would be beneficial comprising administering to said patient an effective dose of a compound of formula (1) as defined above.

Conditions in which inhibition of DHODH is beneficial include: allergy, atopic dermatitis, urticaria, asthma, psoriasis, fibrosis, uveitis, rhinitis, colitis, SLE, autoimmune disease, cystic fibrosis, transplant rejection, graft-v-host disease, non-insulin dependent diabetes, multiple sclerosis, rheumatoid arthritis, sepsis, and parasitic infections such as protozoal infections including malaria, leishmaniasis and trypanosomiasis.

In the treatment of malaria, the compounds of the present invention may be combined with other anti-malarial agents such as proguanil.

According to a further aspect of the present invention there is provided a method of inhibiting DHODH in a patient comprising administering to said patient an effective dose of a compound of formula (1) as defined above.

Preferably the patient is a mammal; more preferably a human.

The amount of a compound of formula (1) required to be effective will, of course, vary and is ultimately at the discretion of the medical or veterinary practitioner. The factors to be considered include the condition being treated, the route of administration, the nature of the formulation, the mammal's body weight, surface area, age and general condition, and the particular compound to be administered. A suitable effective dose is in the range of about 0.01 to about 100 mg/kg body weight, eg 0.1 to about 100 mg/kg body weight, preferably 1-30 mg/kg body weight. The total daily dose may be given as a single dose, multiple doses, e.g., two to six times per day or by intravenous infusion for selected duration. For example, for a 75 kg mammal, the dose range would be about 8 to 900 mg per day, and a typical dose could be about 50 mg per day. If discrete multiple doses are indicated treatment might typically be 15 mg of a compound of formula (I) given up to 4 times per day.

Whilst it is possible for the active compound to be administered alone, it is preferable to

present the active compound in a pharmaceutical formulation. Formulations of the present invention, for medical use, comprise a compound of formula (1) or a salt or physiologically functional derivative thereof together with one or more pharmaceutically acceptable carriers and optionally other therapeutic ingredients. The carrier(s) should be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations according to the present invention include those suitable for oral, topical, rectal or parenteral (including subcutaneous, intramuscular and intravenous) administration. Preferred formulations are those suitable for oral or parenteral administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active compound into association with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier or a finely divided solid carrier or both and then, if necessary, shaping the product into desired formulations.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound; as a powder or granules; or a solution or suspension in an aqueous or non-aqueous liquid such as a syrup, an elixir, an emulsion or a draught.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered active compound with any suitable carrier.

A syrup may be made by adding the active compound to a concentrated, aqueous solution of a sugar, for example sucrose, to which may also be added any accessory ingredients. Such accessory ingredients(s) may include flavourings, an agent to retard crystallisation of the sugar or an agent to increase the solubility of any other ingredients, such as a polyhydric alcohol for example glycerol or sorbitol.

Formulations for rectal administration may be presented as a suppository with a conventional carrier such as cocoa butter.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound which is preferably isotonic with the blood of the recipient. Such formulations suitably comprise a solution of a pharmaceutically and pharmacologically acceptable acid addition salt of a compound of the formula (1) that is isotonic with the blood of the recipient.

Useful formulations also comprise concentrated solutions or solids containing the compound of formula (1) which upon dilution with an appropriate solvent give a solution for parenteral administration as above.

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives (including antioxidants) and the like.

The invention will now be described with reference to the following non-limitative Examples and Figures in which:-

Figure 1 illustrates inhibition of DHODH activity by ethyl 3,4-dimethylpyrrolo [3,2,-b]carbazole-2-carboxylate (Example 1) in crude lysate mitochondrial preparations using a dichlorophenol-indophenol coupled assay.

Figure 2 illustrates the effect of the compound of Example 1 on anti-CD3 induced proliferation of PBMC at cell concentrations a) $1.5 \times 10^5$ cells/well; b) $7.5 \times 10^4$ cells/well; c) $3.75 \times 10^4$ cells/well; and d) $1.87 \times 10^4$ cells/well. Open circles represent day one; solid circles represent day 2; open squares represent day 3; and solid squares represent day 4.

Figure 3 illustrates the effect on cell cycle distribution ($10^6$ cells) over seven days of a) no stimulation; b) anti-CD3 stimulation; c) compound stimulation; and d) anti-CD3 and compound stimulation. Open squares represent G1 phase; open circles represent S phase; solid circles represent G2.M phase.

Figure 4 illustrates the effect of the compound of Example 1 on PPd induced proliferation of PBMC. Open circles relate to no PPd; solid circles relate to PPd at 10 μg/ml;

Figure 5a illustrates the effect of the compound of Example 1 on anti-CD3 induced proliferation of PBMC. Solid squares represent medium control experiment; solid circles represent anti-CD3 at 100 ng/ml; triangles represent anti-CD3 at 100 ng/ml along with the compound at 1μM; and inverted triangles represent anti-CD3 at 100 ng/ml along with the compound at 10μM.

Figure 5b illustrates the effect of the compound of Example 1 on PPd induced proliferation of PBMC. Solid square represent medium control experiment; solid circles represent PPd at 10μg/ml; triangles represent PPd at 10μg/ml along with the compound at 1μM; and inverted triangles represent PPd at 10μg/ml along with the compound at 10μM.

The following examples are provided by way of example only. It will be appreciated that modification of detail may be made without departing from the scope of the invention.

**Example 1 – Ethyl 3,4-Dimethyl[3,2,b]carbazole-2-carboxylate**

Synthesis of this compound is described in published International Patent Application WO94/02483.

**One-pot Synthesis of the Pyrrolocarbazoles – General procedure**

A solution of indole (1.0 mmol) and the 5-acetoxymethyl-4-acetylpyrrole (1.0 mmol) in 1,2-dichloroethane (10 $cm^3$) was heated under gentle reflux and stirred with Montomorillonite K10 clay (1 g) for 3-4 h. The colour of clay turned light brown and the reaction was followed to completion by TLC. After filtration from clay and washing well with 1,2-dichloroethane, evaporation of the combined filtrates gave the pyrrolo[3,2-b]carbazoles which were obtained as yellow crystals after crystallisation

from dichloromethane or ethyl acetate.

**Ethyl 3,4-dimethylpyrrolo[3,2,-b]carbazole-2-carboxylate**

(0.199 g, 65%) was obtained from the reaction of indole and the 5-acetoxymethyl-4-acetylpyrrole.

**Assay for DHODH Inhibitory Activity**

DHODH catalyses the oxidation of dihydroorotate to orotic acid and is the fourth enzyme of the *de novo* pyrimidine biosynthesis pathway, residing on the outer surface of the inner mitochondrial membrane (Jones, M.E. Pyrimidine nucleotide biosynthesis in animals: genes, enzymes, and regulation of ump biosynthesis. Annual Review of Biochemistry, *49:253-79, 1980.* ,35:253-279, 1980.)

DHODH activity was measured in mitochondrial preparations. Crude mitochondrial preparations were obtained as follows: subconfluent DLD-1 cells were harvested and snap-frozen at –70C in PBS. After thawing, cells were washed and resuspended in 0.25M sucrose, 1mM EGTA and 10mM Hepes/NaOH pH7.0. Cells were then homogenised using 25 strokes in a Dounce homogeniser with a tight pestle. Nuclei were pelleted at 1500 x g and a crude mitochondrial pellet was obtained by subsequent centrifugation of the supernatant at 10000 x g. Dihydroorotate dehydrogenase activity was measured in the crude lysates using a dichlorophenol-indophenol coupled assay (Lakaschus, G. and Loffler M. Differential susceptibility of dihydroorotate dehydrogenase/oxidase to brequinar sodium (nsc 368 390) in vitro. Biochemical Pharmacology, *43*: 1025-1030, 1992.)

**Results**

It was found that the compound of Example 1 inhibited DHODH (see Figure 1) with an $IC_{50}$ of 0.4μM.

**Immune Cell Function**

The effect of the compound of Example 1 on polyclonal (anti-CD3) stimulation of PBMC has been studied. The immunopotentiation effect of 1μM of the compound is greatest at low cell concentrations ($1.8 \times 10^4$ cells/well) and results in a 5-fold increase in proliferation above background levels (Figure 2).

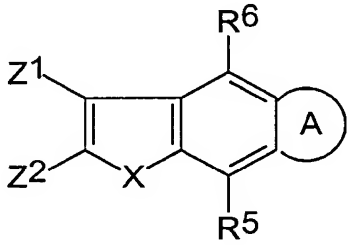
The effect of the compound on anti-CD3 activation of high and low cell concentrations of PBMC was studied. The effect on the cell cycle distribution of cells for up to 7 days following activation was examined and the expression of CD25 on CD4 and CD8 +ve T-cells over the same time period monitored (Figure 3). At high and low density <15% cells accumulated in S phase by day 3-4 in the absence of stimulation, this was elevated to approx 20% in the presence of the compound or anti-CD3 alone. At high cell densities in the presence of anti-CD3 and the compound, approximately 50% of the cells were in S phase by day 4. At low cell densities this figure was reduced to approx 35%. There appeared to be a greater number of blast cells at the lower cell densities. The compound had little effect on the expression of CD25 on CD4 and CD8 +ve T-cells.

The effect of the compound of Example 1 on antigen (PPd) specific stimulation of PBMC has been studied (Figure 4). The compound was found to exhibit a dose dependent effect on PPd induced proliferation. At 10μM the compound of Example 1 was strongly inhibitory of PPd induced proliferation.

To establish whether a dose of 10μM was toxic to PBMC, the kinetics of the response to PPd and anti-CD3 in the presence of the compound at 10 and 1μM was studied. 10μM was not toxic to PBMC in that they were able to mount an effective response to anti-CD3 although that response was less than that seen in the presence of 1μM or its absence. The presence of the compound may prolong the proliferation of anti-CD3 induced cells possibly by preventing the 'burn-out' of proliferating cells. 1μM enhanced proliferation to anti-CD3. In contrast, 10μM almost completely inhibited the proliferation of PBMC to PPd whereas 1μM had little effect. Therefore 10μM of the compound of Example 1 is not toxic to immune cells but this dose has a profound inhibitory effect on the immunocompetence of cells in response to an antigen specific stimulation.

CLAIMS:

1. Use of a compound of formula (1) in the manufacture of a medicament for use as an immunomodulatory or anti-inflammatory drug or for use in the treatment of a therapeutic indication in which inhibition of dehydro-orate dehydrogenase (DHODH) is beneficial:-



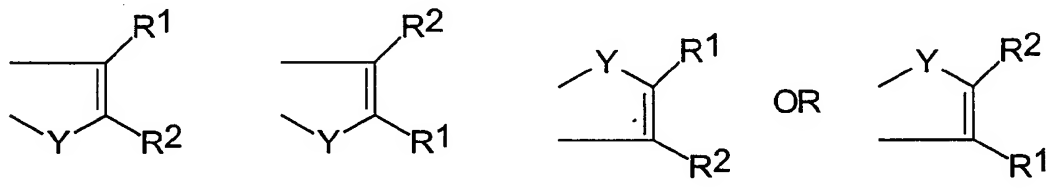

(1)

and salts and physiologically functional salts thereof,

wherein X is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$, wherein $R^7$ is H or the following groups which may be optionally substituted: cyloalkyl, cycloalkenyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, acyl, aroyl, sulphonyl, alkylsulphonyl, arylsulphonyl or COOR;

$R^5$ and $R^6$ are independently selected from H, hydroxy, nitro, amino, halo, cyano, CHO, $COR^8$, $CO_2R^8$ and the following groups which may be optionally substituted: alkyl, aryl, aryloxy, aralkyloxy, alkoxy, aralkyl, wherein $R^8$ is optionally substituted alkyl and aryl;

A is:




wherein $R^1$ is $COR^8$, CHO, $CH_2OH$, $CH_2OR^8$, $CONH_2$, $COOR^8$, $CONHR^8$, $CONR^8R^8$, $CONHNR^8R^8$, $COO(CH_2)_nNR^8R^8$, $CSOR^8$, $CSSR^8$, $COSR^8$, $CSNHR^8$, $CSNR^8$ $R^8$,

$CNHOR^8$ or an optionally substituted 5 or 6 membered aromatic or nonaromatic heterocyclic ring containing 1 to 4 heteroatoms,

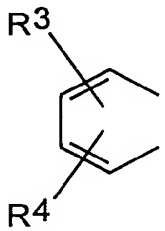
wherein the groups $R^8$ are independently selected from hydrogen, optionally substituted alkyl, aryl, aralkyl, acyl, alkoxyalkyl, heterocycloalkyl and heteroaralkyl groups, and $C_{1-10}$ optionally substituted hydrocarbyl groups which may contain one or two oxygen atoms in the chain and wherein n is 1 to 4;

or $R^8$ may independently be sugar groups;

$R^2$ is H, hydroxy, haloalkyl, halo, cyano, $COOR^8$, alkyl, aryl, alkenyl, alkynyl, alkoxy, (wherein alkyl, aryl, alkenyl, alkynyl and alkoxy can be substituted) $CH_2CH_2CO_2R^9$ (wherein $R^9$ is alkyl or aryl), CHO, $COR^8$, $COOR^8$ or a $C_{1-10}$ optionally substituted hydrocarbyl group which may contain one or two oxygen atoms in the chain, wherein $R^8$ is independently selected from the groups defined for $R^8$ above;

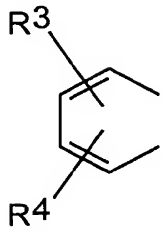
Y is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$ wherein $R^7$ is independently selected from groups hereinbefore defined for $R^7$;

$Z^1$ and $Z^2$ are independently selected from H, halogen, cyano, amino, alkyl, $COOR^8$, $CONHR^8$, $COR^8$, $CH_2OH$, $CH_2OR^8$, $CONH_2$, CON $R^8R^8$, $CSOR^8$, $CSSR^8$, $COSR^8$, $CSNHR^8$, $CSNR^8R^8$ and $CNHOR^8$ wherein $R^8$ is independently selected from the groups defined for $R^8$ above; or $Z^1$ and $Z^2$ together form the group:




wherein $R^3$ and $R^4$ are independently selected from H, hydroxy, alkyl, haloalkyl, alkoxy, halo, cyano, azido, nitro, amino, alkyl amino, dialkyl amino, CHO, $COR^8$, $CONHR^8$, CON $R^8R^8$ (wherein $R^8$ is independently selected from the groups defined for $R^8$ above ),carboxyl or $CO_2R^{10}$, wherein $R^{10}$ is independently selected from alkyl, aralkyl and aryl.

2. Use of a compound according to claim 1, wherein $Z^1$ and $Z^2$ together form the group:



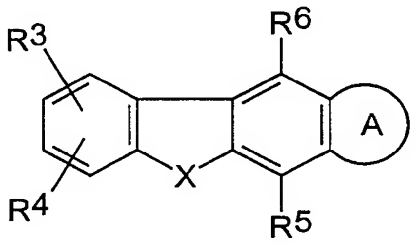

wherein $R^3$ and $R^4$ are independently selected from H, hydroxy, alkyl, haloalkyl, alkoxy, halo, cyano, azido, nitro, amino, alkyl amino, dialkyl amino, CHO, $COR^8$, $CONHR^8$, $CON R^8R^8$ (wherein $R^8$ is independently selected from the groups defined for $R^8$ above ),carboxyl or $CO_2R^{10}$, wherein $R^{10}$ is independently selected from alkyl, aralkyl and aryl.

3. Use of a compound according to claim 2, wherein

X is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$, wherein $R^7$ is H, alkyl, aralkyl, aryl, alkenyl, acyl, alkynyl, sulphonyl or substituted sulphonyl; and

Y is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$.

4. Use of a compound according to claim 3 wherein the compound is of formula (II)




(II)

and salts and physiologically functional derivatives thereof,

wherein A is as hereinbefore defined,

X is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$, wherein $R^7$ is H, alkyl, aralkyl, aryl, alkenyl, acyl, alkynyl, sulphonyl or substituted sulphonyl;

Y is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$;

$R^1$ is $COR^{11}$, $COOR^{11}$, CHO, $CH_2OH$, $CH_2OR^{12}$, $CONH_2$, $CONHR^{13}R^{14}$, $CONHR^{13}$, $CONR^{13}R^{14}$, $COO(CH_2)_nNR^{13}R^{14}$, wherein $R^{11}$ is H, alkyl, aryl, substituted aryl or aralkyl, $R^{12}$ is acyl or substituted acyl, $R^{13}$ and $R^{14}$ are independently hydrogen, alkyl or aryl, and n is 1 to 4 carbon atoms;

$R^2$ is H, $COOR^{11}$, alkyl, aryl, substituted aryl or $CH_2CH_2CO_2R^9$ wherein $R^9$ is alkyl or aryl;

$R^3$ and $R^4$ are independently H,hydroxy, alkyl, haloalkyl, alkoxy, halo, cyano, nitro, amino, alkyl amino, dialkyl amino, substituted alkyl, carboxyl or $CO_2R^9$;

$R^5$ is H, alkyl, substituted alkyl, aralkyl, nitro, amino, halo, cyano, CHO, $COOR^{11}$;

$R^6$ is H, aryl, alkyl, aralkyl, nitro, halogen, CHO or $COR^{15}$ wherein $R^{15}$ is alkyl or aryl.

5. Use of a compound according to claim 4 wherein the compound is selected from

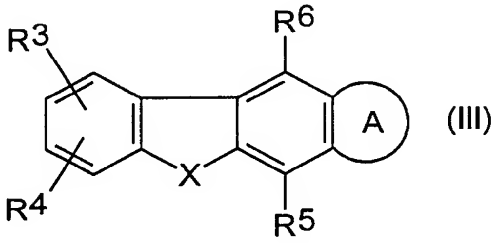
3-Pyridyl 3, 4-dimethylpyrrolo( 3, 2-b] carbazole-2-carboxylate
[(3-Dimethylamino)phenyl]3, 4-dimethylpyrrolo[3,2-b] carbazole-2-carboxylate
Benzyl 1, 3, 4- trimethylpyrrolo( 3, 2-b] carbazole-2-carboxylate
Phenyl 3, 4-dimethylpyrrolo[ 3, 2-b] carbazole-2-carboxylate
3,4-Dimethyl-2-( 1-imidazolylcarbonyl ) pyrrolo [3, 2-b] carbazole
Ethyl 3, 4-dimethylpyrrolo [3,2,-b]carbazole-2-carboxylate;
Ethyl 3, 4-dimethylbenzothieno [4, 5-f] indole-2-carboxylate;
Benzyl 3, 4-dimethylpyrrolo [3, 2-b] carbazole-2-carboxylate;
Benzyl 8-f luoro-3, 4-dimethylpyrrolo [3,2-b] carbazole-2-carboxylate;
Ethyl 8-f luoro-3, 4-dimethylpyrrolo [3,2-b] carbazole-2-carboxylate

Benzyl 3,4, 6-trimethylpyrrolo (3, 2-b] carbazole-2-carboxylate;
Ethyl 3,4, 6-trimethylpyrrolo [3, 2-b] carbazole-2-carboxylate;
8-Fluoro-3, 4-dimethylpyrrolo[ 3, 2-b] carbazole-2-carboxylic acid
3,4-Dimethylpyrrolo[ 3, 2-_b] carbazole-2-carboxylic acid;
Ethyl 8-methoxy-3,4-dimethylpyrrolo [3, 2-b] carbazole-2-carboxylate;
3,4,6-Trimethylpyrrolo [3, 2-b] carbazole-2-carboxylic acid and
Benzyl 8-methoxy-3, 4-dimethylpyrrolo [3, 2-_b] carbazole-2-carboxylate;

and physiologically functional derivatives thereof.

6. Use of a compound according to claim 1 wherein the compound is ethyl 3,4-dimethylpyrrolo [3,2-b]carbazole-2-carboxylate or a physiologically functional derivative thereof.

7. Use of a compound according to claim 1 wherein the compound is of the formula (III)



(III)

and salts and physiologically functional derivatives thereof,
wherein A is as hereinbefore defined,

X is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$, wherein $R^7$ is H, alkyl, aralkyl, aryl, alkenyl, acyl, alkynyl, sulphonyl or substituted sulphonyl;
Y is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$;

$R^1$ is $COOR^{16}$, $CONHR^{16}$, $CONR^{16}R^{17}$, $CSOR^{16}$, $CSSR^{16}$, $COSR^{16}$, $CSNHR^{16}$,

$CSNR^{16}R^{17}$, $CNHOR^{16}$ wherein $R^{16}$ and $R^{17}$ are independently $C_{1-10}$ optionally substituted hydrocarbyl groups which may optionally contain one or two oxygen atoms in the chain; or $R^{16}$ and $R^{17}$ are independently alkoxyalkyl, heterocycloalkyl, heteroaralkyl,

or $R^{16}$ and $R^{17}$ may independently be sugar groups;

$R^2$ is H, halo, cyano, $COOR^{16}$, alkyl, aryl, alkenyl, alkynyl, alkoxy, (wherein alkyl, aryl, alkenyl, alkynyl and alkoxy can be substituted) or $CH_2CH_2CO_2R^9$ wherein $R^9$ is alkyl or aryl;

$R^3$ and $R^4$ are independently H,hydroxy, alkyl, haloalkyl, alkoxy, halo, cyano, nitro, amino, alkyl amino, dialkyl amino, substituted alkyl, carboxyl or $CO_2R^9$;

$R^5$ is H, hydroxy, aryloxy, aralkyloxy, alkyl, substituted alkyl, aralkyl, nitro, amino, halo, cyano, CHO; and

$R^6$ is H, aryl, alkyl, aralkyl, nitro, halogen, CHO or $COR^{15}$ wherein $R^{15}$ is alkyl or aryl.

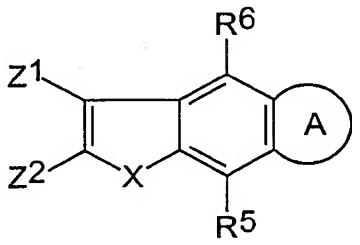
8. Use of a compound according to claim 1 wherein the compound is selected from:-

[(2-Dimethylamino)ethyl] 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(2-Methylsulphonylethyl) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(2-Methylsulphinylethyl) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(1,3-Dibenzyloxypropyl-2) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(1-Benzyloxy-3-hydroxypropyl-2) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(1,3-Dihydroxypropyl-2) 3,4-dimethyl-pyrrolo[3,2-b]carbazole-2-carboxylate
(2-Amino-2-methylpropyl-1) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(4-Nitrophenylmethyl) 2-(3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxy)acetate
2-(3,4-Dimethylpyrrolo[3,2-b]carbazole-2-carboxy)acetic acid
Cyclohexyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
Cyclohexylmethyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
Cyclopentyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
Cyclooctyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
3,5-Di(tert-butyldiphenylsilyloxy)cyclohexyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-

carboxylate
3,5-Dihydroxycyclohexyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
cis-4-tert-Butyldiphenylsilyloxycyclohexyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
cis-4-Hydroxycyclohexyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
trans-4-tert-Butyldiphenylsilyloxycyclohexyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
trans4-Hydroxycyclohexyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
Tetrahydro-2H-pyran4-yl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
1-Benzylpiperidin-4-yl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
Piperidin-4-yl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
1-Methylpiperidin-4-yl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(3,4-Dimethylpyrrolo[3,2-b]2-carbazolyl)3-O-( 1,2:5,6-di-O-isopropylidene glucofuranoside)
(3,4-Dimethylpyrrolo[3,2-b]2-carbazolyl) 3-O-(1,2-O-isopropyl-ideneglucofuranoside)
[3-(4-Nitrophenylmethoxy)phenyl] 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(3-Hydroxyphenyl) 3-4,-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(4-Phthalamidophenyl) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
4-(Aminophenyl) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(4-Nitrophenylmethyl) 3-(3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxy)benzoate
3-(3,4-Dimethylpyrrolo[3,2-b]carbazole-2-carboxy)benzoic acid
3-(tert-Butyldiphenylsilyloxymethyl)phenyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(3-Hydroxymethyl)phenyl 3 ,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
[3-(4-Nitrophenylmethoxy)phenyl] 4-methyl-1H-[1]benzothieno[2,3 –f]indole-2-carboxylate
(3-Hydroxyphenyl)4-methyl 1H-[1]benzothieno[2,3-f]indole-2-carboxylate
3-(4-Nitrophenylmethoxy)phenylmethyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
3-(tert-Butyldiphenylsilyloxyphenyl)methyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(3-Hydroxyphenyl)methyl 3 ,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxylate
(1-Hydroxy-3-methylpropyl-2) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxamide
2-Hydroxyethyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxamide
2-Chloroethyl 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxamide
N-(2-Aminoethyl) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxamide
N-(2-Acetamidoethyl) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxamide
(3-Aminopropyl- 1) 3,4-dimethylpyrrolo[3,2-b]carbazole-2-carboxamide
2-Hydroxyethyl 4-methyl- 1H-[1]benzothieno[2,3-f]indole-2-carboxamide

2-Chloroethyl 4-methyl-1H-[1]benzothieno[2,3-f]indole-2-carboxamide and physiologially functional derivatives thereof.

9. Use of a compound according to claim 1 wherein the compound is of the formula (V)




(V)

or a salt or physiologically functional derivative thereof,

wherein A is as hereinbefore defined

X is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$, wherein $R^7$ is H, alkyl, aralkyl, aryl, alkenyl, acyl, alkynyl, sulphonyl, substituted sulphonyl, or COOMe;

Y is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$;

$R^1$ is $COR^{18}$, CHO, $CH_2OH$, $CH_2OR^{18}$, $CONH_2$, $COOR^{18}$, $CONHR^{18}$, $CONR^{18}R^{19}$, $CSOR^{18}$, $CSSR^{18}$, $COSR^{18}$, $CSNHR^{18}$, $CSNR^{18}R^{19}$, $CNHOR^{18}$ wherein $R^{18}$ and $R^{19}$ are independently hydrogen, alkoxyalkyl, heterocycloalkyl, heteroaralkyl, or $C_{1-10}$ optionally substituted hydrocarbyl group which may optionally contain one or two oxygen atoms in the chain;

or $R^{18}$ and $R^{19}$ may independently be sugar groups;

$R^2$ is H, halo, cyano, $COOR^{18}$, alkyl, aryl, alkenyl, alkynyl, alkoxy, (wherein alkyl, aryl, alkenyl, alkynyl and alkoxy can be substituted) or $CH_2CH_2CO_2R^9$ wherein $R^9$ is alkyl or aryl;

$Z^1$ is H, alkyl, halogen, cyano, amino, $COOR^{18}$, $CONHR^{18}$, $COR^{18}$, $CH_2OH$, $CH2OR^{18}$, $CONH_2$, $CONR^{18}R^{19}$, $CSOR^{18}$, $CSSR^{18}$, $COSR^{18}$, $CSNHR^{18}$, $CSNR^{18}R^{19}$ or $CNHOR^{18}$;

$Z^2$ is H, halogen, cyano, amino, alkyl, $COOR^{18}$, $CONHR^{18}$, $COR^{18}$, $CH_2OH$, $CH_2OR^{18}$, $CONH_2$, $CONR^{18}R^{19}$, $CSOR^{18}$, $CSSR^{18}$, $COSR^{18}$, $CSNHR^{18}$, $CSNR^{18}R^{19}$ or $CNHOR^{18}$;

$R^5$ is H, hydroxy, aryloxy, aralkyloxy, alkyl, substituted alkyl, aralkyl, nitro, amino, halo, cyano, $COOR^{18}$ or CHO;

$R^6$ is H, aryl, alkyl, aralkyl, nitro, halogen, CHO or $COR^{20}$ wherein $R^{20}$ is alkyl or aryl.

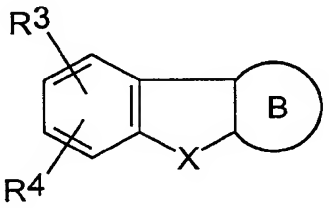
10. Use of a compound according to claim 9 wherein the compound is selected from:-

Ethyl 1,7-dihydro-3,4,6-trimethylpyrrolo[3,2-f]indole-2-carboxylate;
Diethyl 1,7-dihydro-3,4,6-trimethylpyrrolo[3,2-f] indole-2,5-dicarboxylate; and
Ethyl 6-methoxycarbonyl-3,4-dimethylpyrrolo [3,2-f]indole-2-carboxylate

and physiologically functional derivatives thereof; and

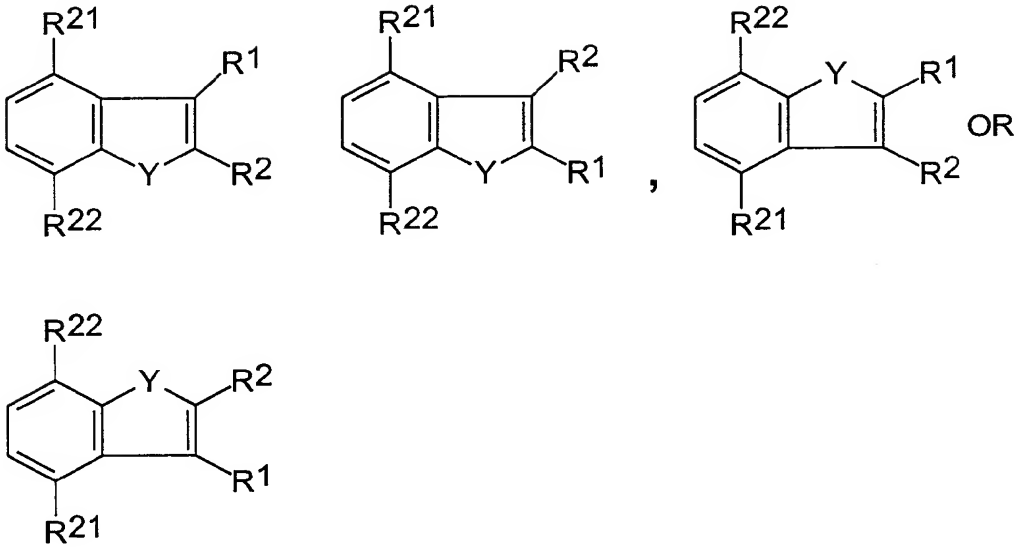
Ethyl 6-Benzyloxycarbonyl-3,4-dimethylpyrrolo[3,2-f ]indole-2-carboxylate;
Dibenzyl 3,4-dimethylpyrrolo[3,2-f]indole-2,6-dicarboxylate;
Ethyl 7-methoxycarbonyl-3,4-dimethylpyrrolo [3,2-f]indole-2-carboxylate; and
Ethyl 3,4-dimethylpyrrolo[3,2-f]indole-2-carboxylate
and physiologically functional derivatives thereof.

11. Use of a compound according to claim 1 wherein the compound is of the formula (VI)



(VI)

and salts and physiologically functional derivative thereof,
wherein B is



X is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$, wherein $R^7$ is H or the following groups which may be optionally substituted: cyloalkyl, cycloalkenyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, acyl, aroyl, alkylsulphonyl or arylsulphonyl;

Y is O, S, SO, $SO_2$, $CH_2$, CO or $NR^7$;

$R^1$ is an optionally substituted 5- or 6-membered heterocyclic ring containing 1 to 4 heteroatoms wherein the 5- or 6- membered ring may be aromatic or non-aromatic;

$R^2$ is H, hydroxy, halo, haloalkyl, cyano, alkyl, aryl, alkenyl, alkynyl, alkoxy, (wherein alkyl, aryl, alkenyl, alkynyl, and alkoxy can be substituted), CHO, $COR^{23}$, $COOR^{23}$ wherein $R^{23}$ is hydrogen or is a $C_{1-10}$ optionally substituted hydrocarbyl group which may contain one or two oxygen atoms;

$R^3$ and $R^4$ are independently H, hydroxy, alkyl, haloalkyl, azido, CHO, $COR^{23}$, $CO_2R^{23}$, $CONHR^{23}$, $CONR^{23}R^{24}$, alkoxy, halo, cyano, nitro, amino, alkyl amino, dialkyl amino, carboxyl wherein $R^{24}$ is alkyl, aryl or aralkyl;

$R^{21}$ is H, hydroxy, nitro, amino, halo, cyano, CHO, $COR^{23}$, or the following groups which may be optionally substituted: alkyl, aryl, aryloxy, aralkyloxy, alkoxy, aralkyl;

$R^{22}$ is H, hydroxy, amino, nitro, halo, CHO, $COR^{25}$, $CO_2R^{25}$ wherein $R^{25}$ is optionally substituted alkyl or aryl, or $R^6$ is alkyl, aralkyl, or aryl wherein alkyl, aralkyl or aryl may be optionally substituted.

12. Use of a compound according to claim 11 wherein the compound is selected from:-

3,4-Dimethyl-2-(3-ethyl-1,2,4-oxadiazol-5-yl) pyrrolo[3,2-*b*]carbazole;
2-(3-Benzyl- 1,2,4-oxadiazol-5-yl)-3,4-dimethylpyrrolo[3,2-*b*]carbazole;
3,4-Dimethyl-2-(3-ethyl-1,2,4-oxadiazol-5-yl) pyrrolo[2,3-*b*]carbazole;
2-(3-ethyl-1,2,4-oxadiazol-5-yl)-4-methyl-1*H*-[1]benzothieno[2,3-*f*]indole;
3,4-Dimethyl-2-(2-methyl-1,3,4-oxadiazol-5-yl)-pyrrolo[3,2-*b*]carbazole;
3,4-Dimethyl-2-(2-ethyl-1,3,4-oxadiazol-5-yl)-pyrrolo[3,2-*b*]carbazole;
3,4-Dimethyl-2-(2-phenyl-1,3,4-oxadiazol-5-yl)-pyrrolo[3,2-*b*]carbazole;
2-(2-Ethyl-1,3,4-oxadiazol-5-yl)4-methyl-1*H*-[1]benzothieno[2,3-*f*]indole;
3,4-Dimethyl-2-[3-(3,4-methylenedioxyphenyl)-1,2,4-oxadiazol-5-yl]pyrrolo[3,2-*b*]carbazole;
4-Methyl-2-(2-oxazolin-2-yl)-1H-[1]benzothieno[2,3-*f*]indole
3,4-Dimethyl-2-(3-methyl-1,2,4-oxadiazol-5-yl)pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-(3-methyl-1,2,4-oxadiazol-5-yl)pyrrolo[2,3-*b*]carbazole
3,4-Dimethyl-2-[(3-phenyl)-1,2,4-oxadiazol-5-yl]pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-(2-oxazolin-2-yl)pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-[3-(1-piperidinylmethyl)-1,2,4-oxadiazol-5-yl)pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-[3-(4-pyridyl)-1,2,4-oxadiazol-5-yl]pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-(3-methoxymethyl-1,2,4-oxadiazol-5-yl)pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-[3-(2-hydroxyethyl)-1,2,4-oxadiazol-5-yl]pyrrolo[3,2-*b*]carbazole
2-(3-Ethyl- 1,2,4-oxadiazol-5-yl)4--methyl- 1*H*-[1]benzofuro[2,3-*f*]indole
3,4-Dimethyl-2-(4,4-dimethyl-2-oxazolin-2-yl)pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-[3-(3-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-[3-(N,N-dimethylaminomethyl)-1,2,4-oxadiazol-5-yl]pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-(tetrazol-5-yl)pyrrolo[3 ,2-b]carbazole)
3,4-Dimethyl-2-[3-(4-morpholinomethyl)-1,2,4-oxadiazol-5-yl)pyrrolo[3,2-b]carbazole
3,4-Dimethyl-2-(3-methoxyethyl- 1,2,4-oxadiazol-5-yl)pyrrolo[3,2-*b*]carbazole
3,4-Dimethyl-2-(1,2,4-oxadiazol-5-yl)pyrrolo[3,2-*b*]carbazole

and salts and physiologically functional derivatives thereof.

13. Use of a compound as defined in any one of claims 1 to 12 in the manufacture of a medicament for use as an immunomodulating drug.

14. Use of a compound as defined in any one of claims 1 to 12 in the manufacture of

a medicament for use as an immunosuppressive drug.

15. Use of a compound as defined in any one of claims 1 to 12 in the manufacture of a medicament for use as an anti-inflammatory drug

16. Use of a compound as defined in any one of claims 1 to 12 in the manufacture of a medicament for use in the treatment of a therapeutic indication in which inhibition of DHODH is beneficial.

17. Use of a compound as defined in any one of claims 1 to 12 in the manufacture of a medicament for use as a DHODH inhibitor.

18. A method of treating a patient requiring immunomodulation comprising administering to said patent an effective dose of a compound as defined in any one of claims 1 to 12.

19. A method of treating a patient requiring immunosuppression comprising administering to said patent an effective dose of a compound as defined in any one of claims 1 to 12.

20. A method of treating a patient requiring anti-inflammatory treatment comprising administering to said patent an effective dose of a compound as defined in any one of claims 1 to 12.

21. A method of treating a patient having a condition in which inhibition of DHODH would be beneficial comprising administering to said patent an effective dose of a compound as defined in any one of claims 1 to 12.

22. A method of inhibiting DHODH in a patient comprising administering comprising administering to said patent an effective dose of a compound as defined in any one of claims 1 to 12.

FIG. 1

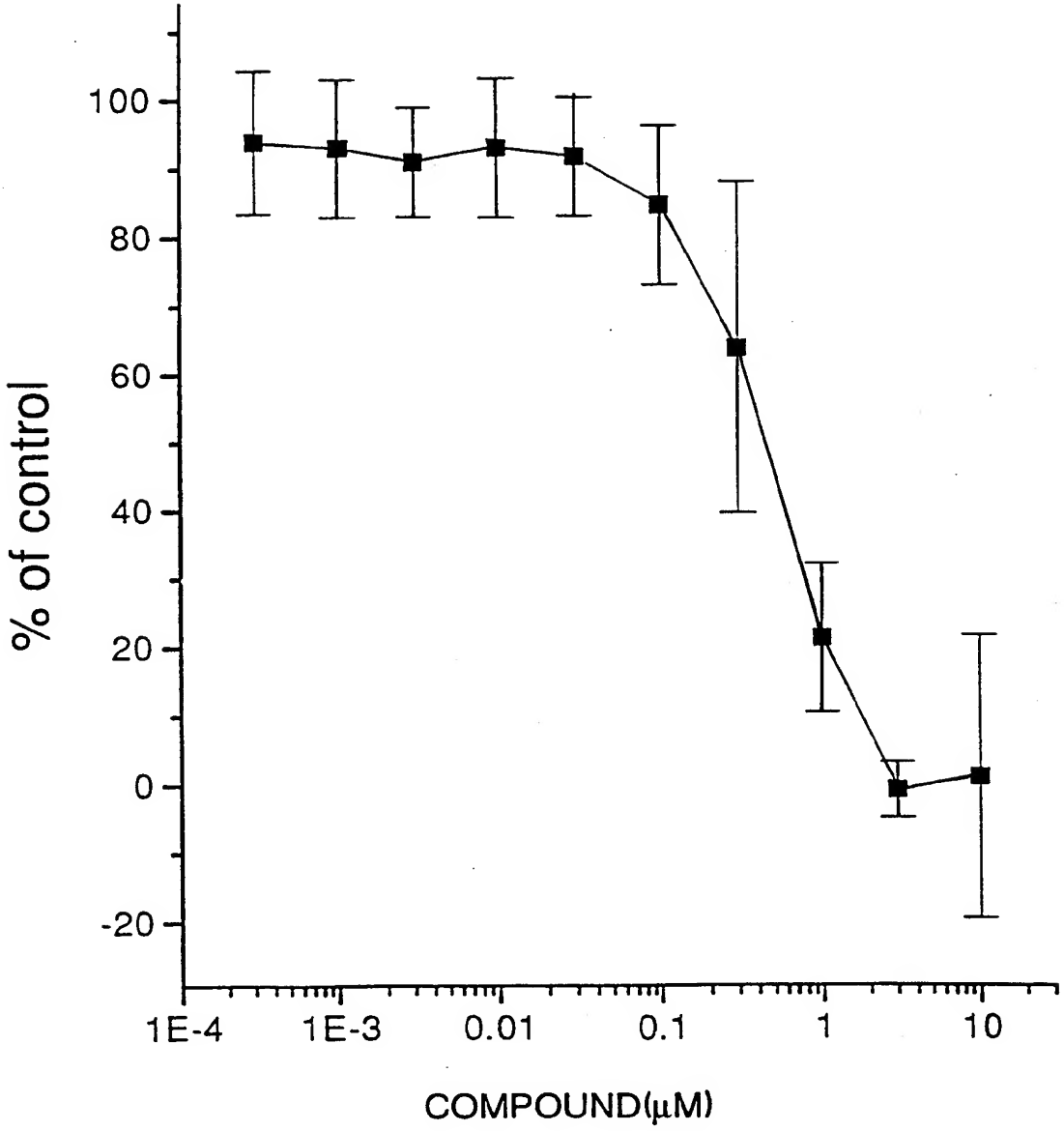


FIG. 2(a)

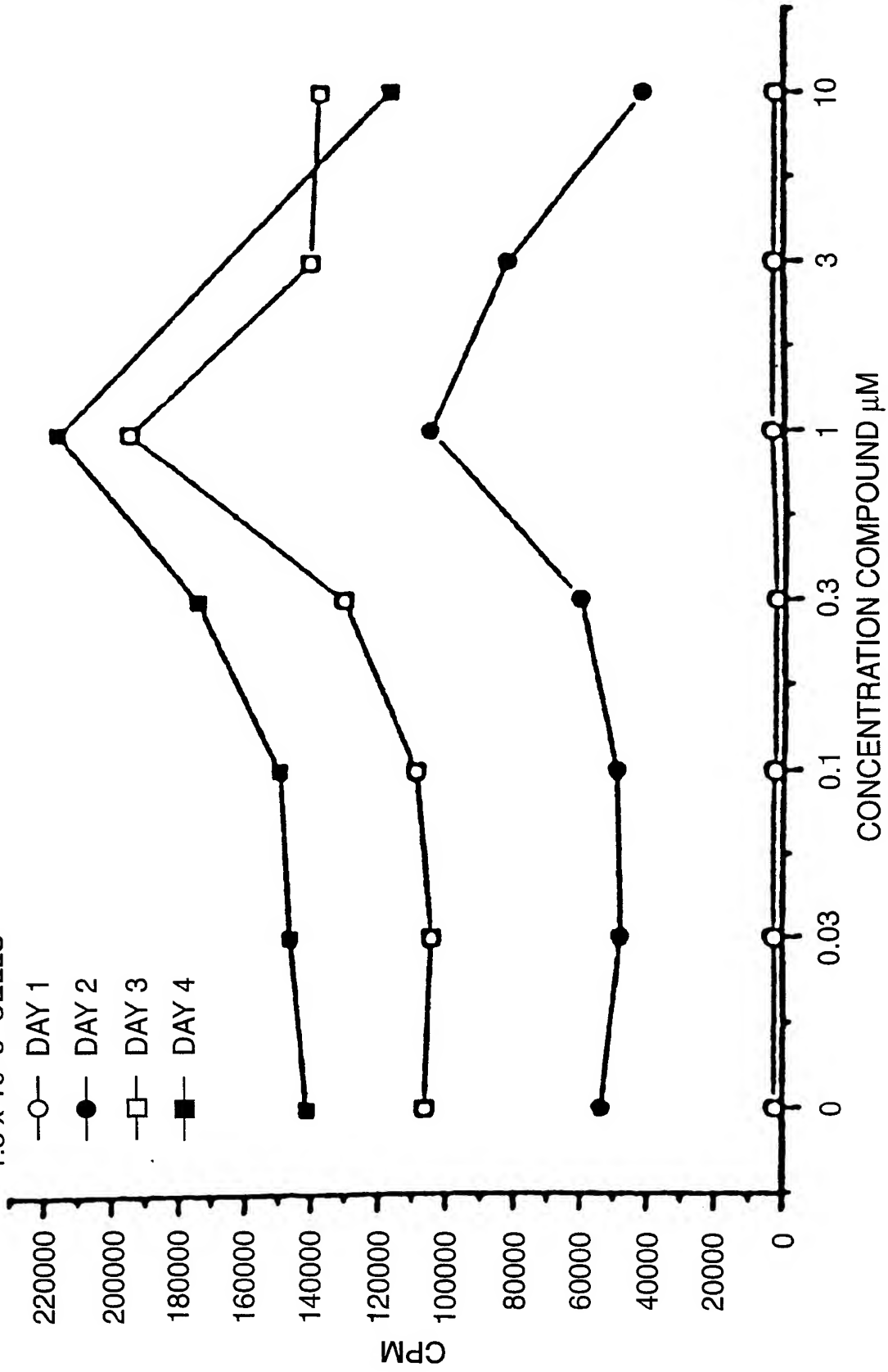

1.5 x 10^5 CELLS
DAY 1
DAY 2
DAY 3
DAY 4
CPM
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
0
0.03
0.1
0.3
1
3
10
CONCENTRATION COMPOUND µM

FIG. 2(b)

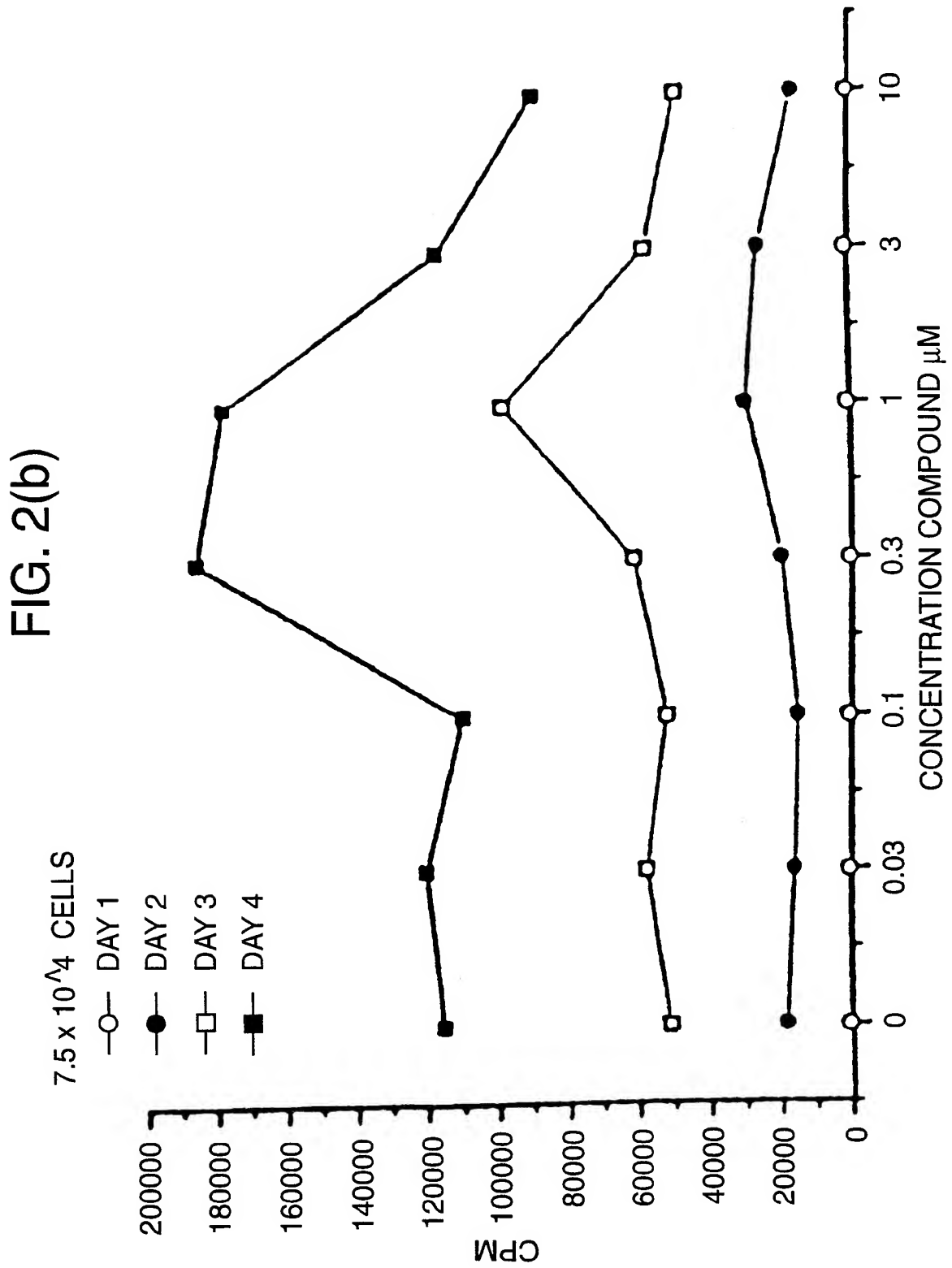

7.5 x 10^4 CELLS
DAY 1
DAY 2
DAY 3
DAY 4
CPM
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
0
0.03
0.1
0.3
1
3
10
CONCENTRATION COMPOUND µM

FIG. 2(c)

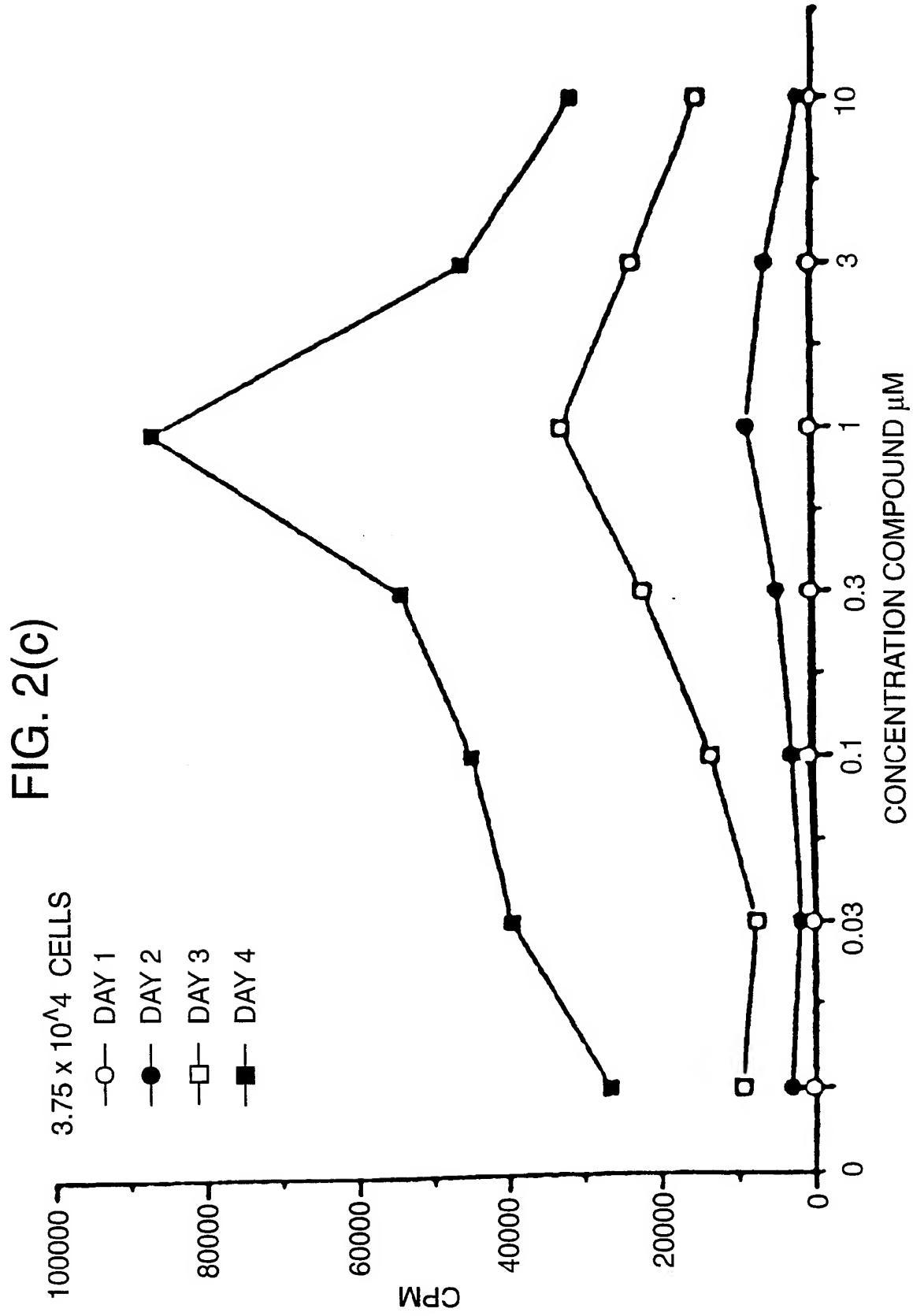

3.75 x 10^4 CELLS
DAY 1
DAY 2
DAY 3
DAY 4
CPM
100000
80000
60000
40000
20000
0
0
0.03
0.1
0.3
1
3
10
CONCENTRATION COMPOUND µM

FIG. 2(d)

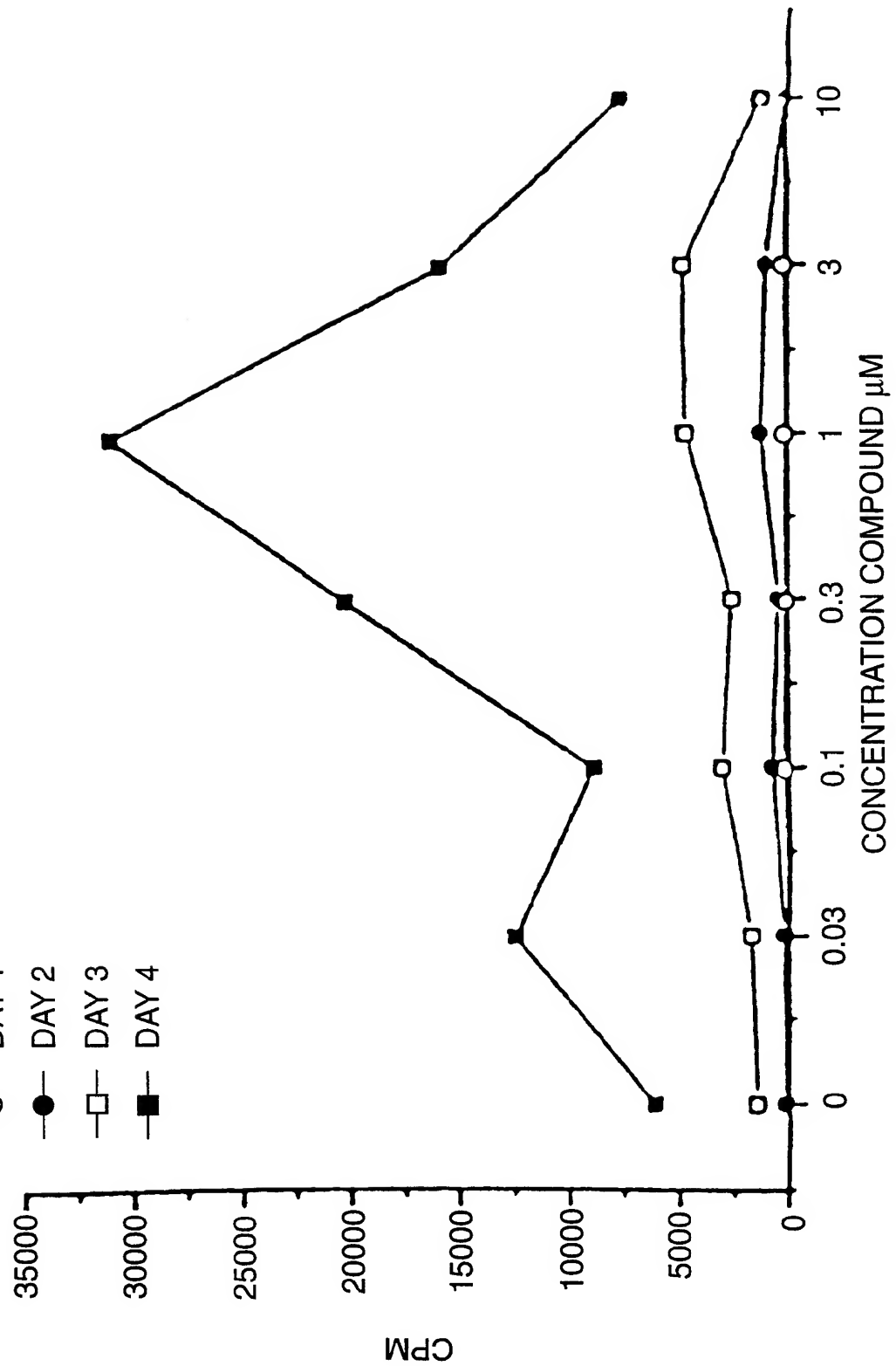

1.87 x 10^4 CELLS
DAY 1
DAY 2
DAY 3
DAY 4
CPM
35000
30000
25000
20000
15000
10000
5000
0
0
0.03
0.1
0.3
1
3
10
CONCENTRATION COMPOUND µM

FIG. 3(a)

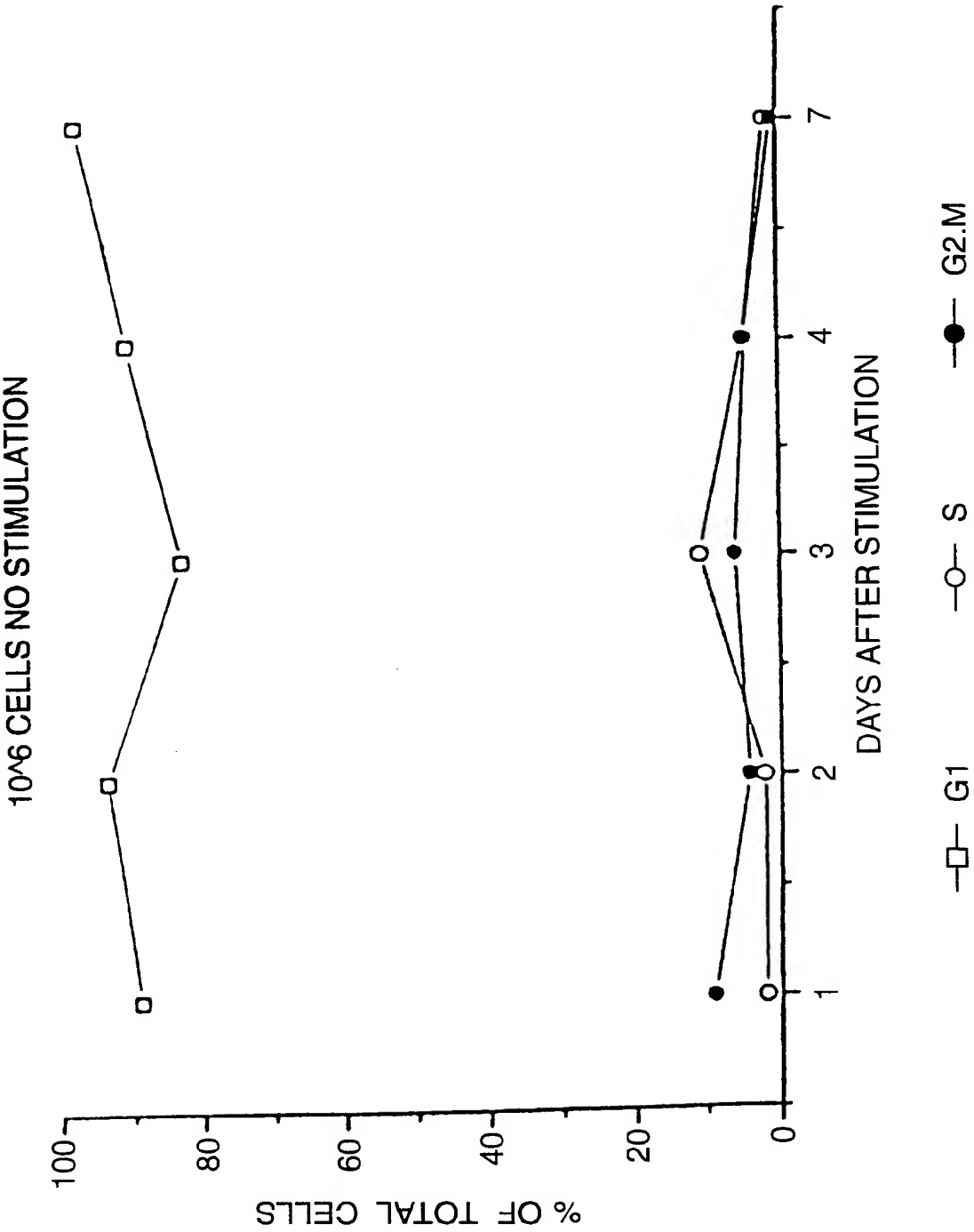

10^6 CELLS NO STIMULATION
% OF TOTAL CELLS
100
80
60
40
20
0
1
2
3
4
7
DAYS AFTER STIMULATION
G1
S
G2.M

FIG. 3(b)

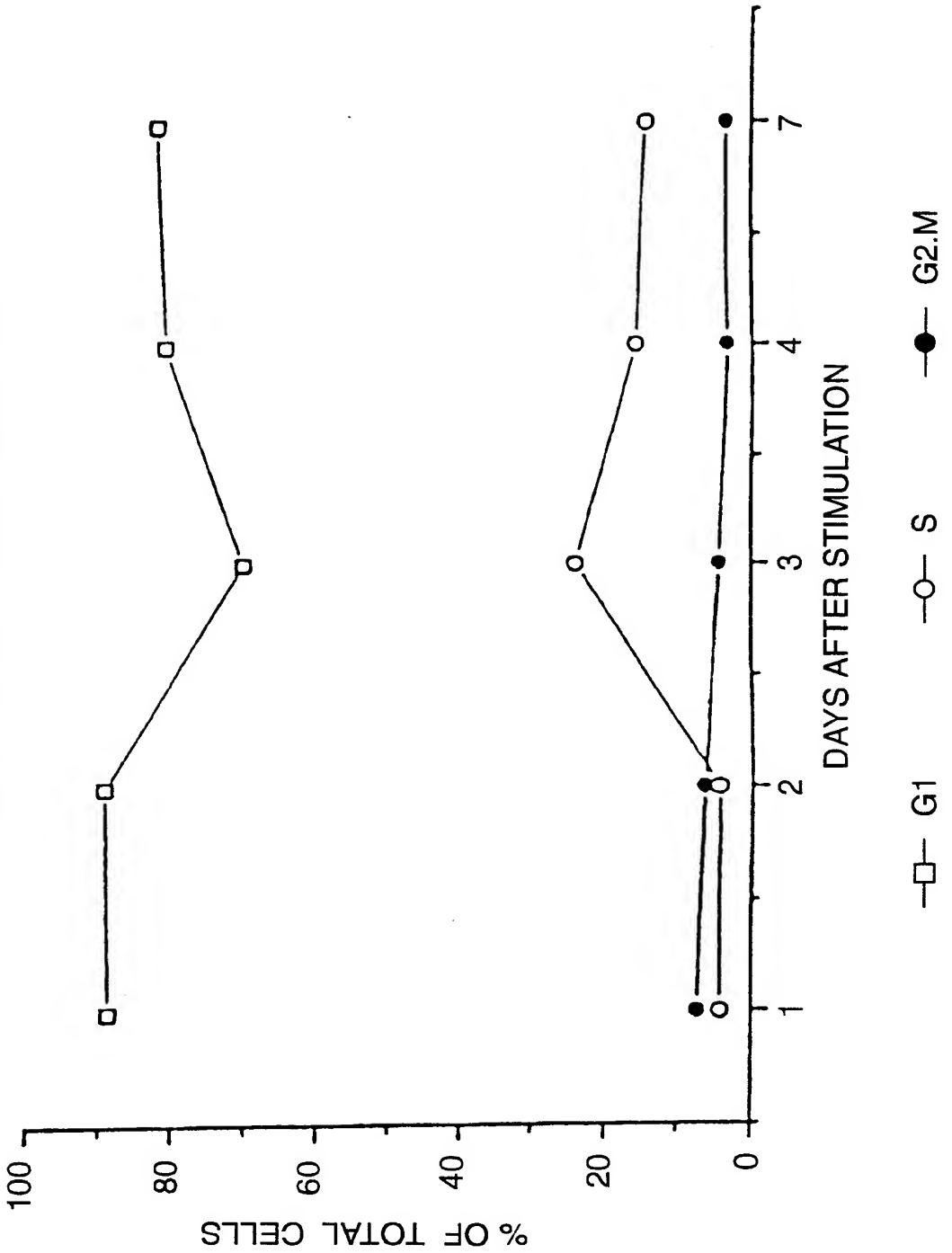

10^6 CELLS ANTI-CD3 STIMULATION
% OF TOTAL CELLS
100
80
60
40
20
0
1
2
3
4
7
DAYS AFTER STIMULATION
G1
S
G2.M

FIG. 3(c)

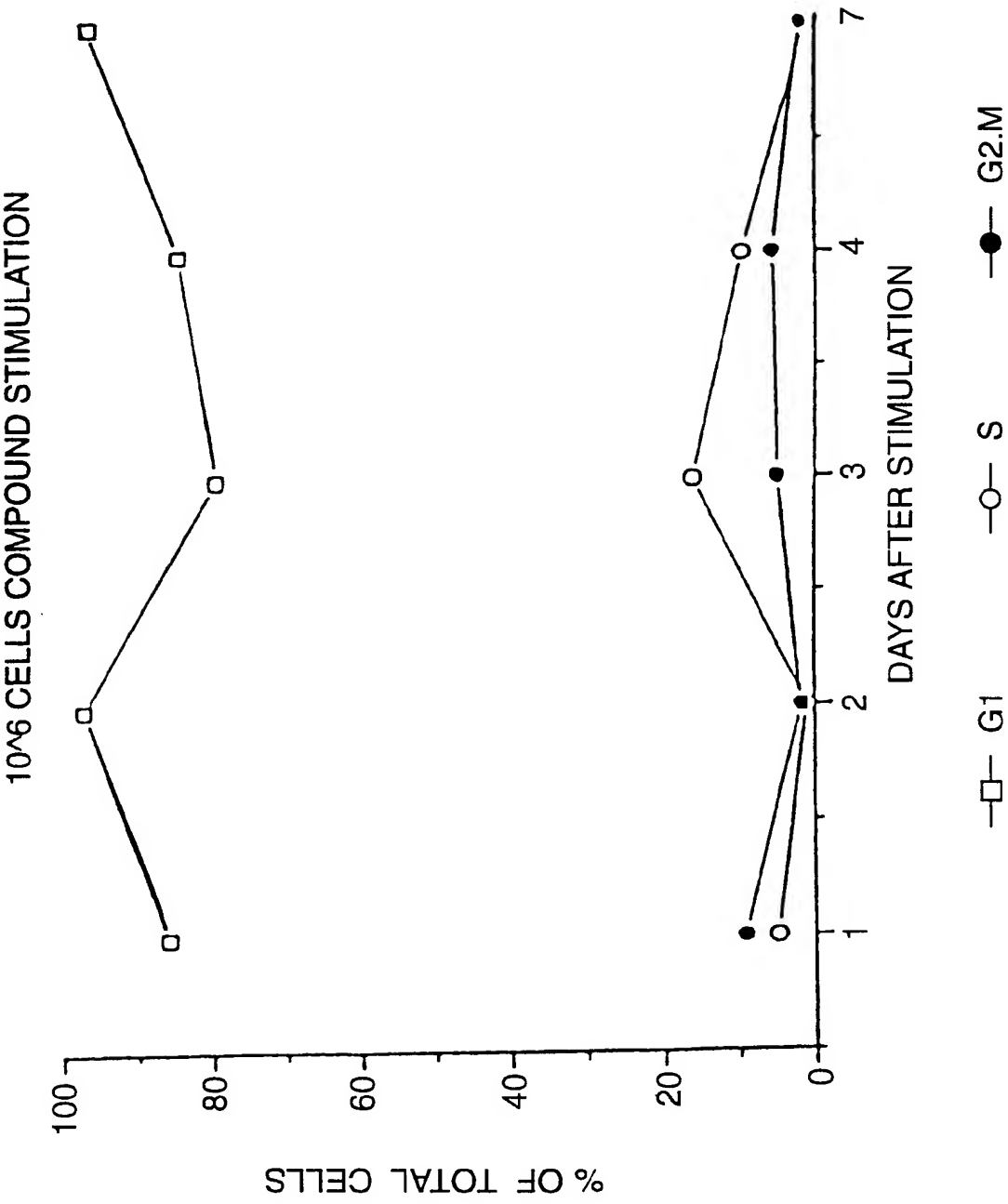

10^6 CELLS COMPOUND STIMULATION
% OF TOTAL CELLS
100
80
60
40
20
0
1
2
3
4
7
DAYS AFTER STIMULATION
G1
S
G2.M

FIG. 3(d)

10^6 CELLS ANTI-CD3 + COMPOUND STIMULATION

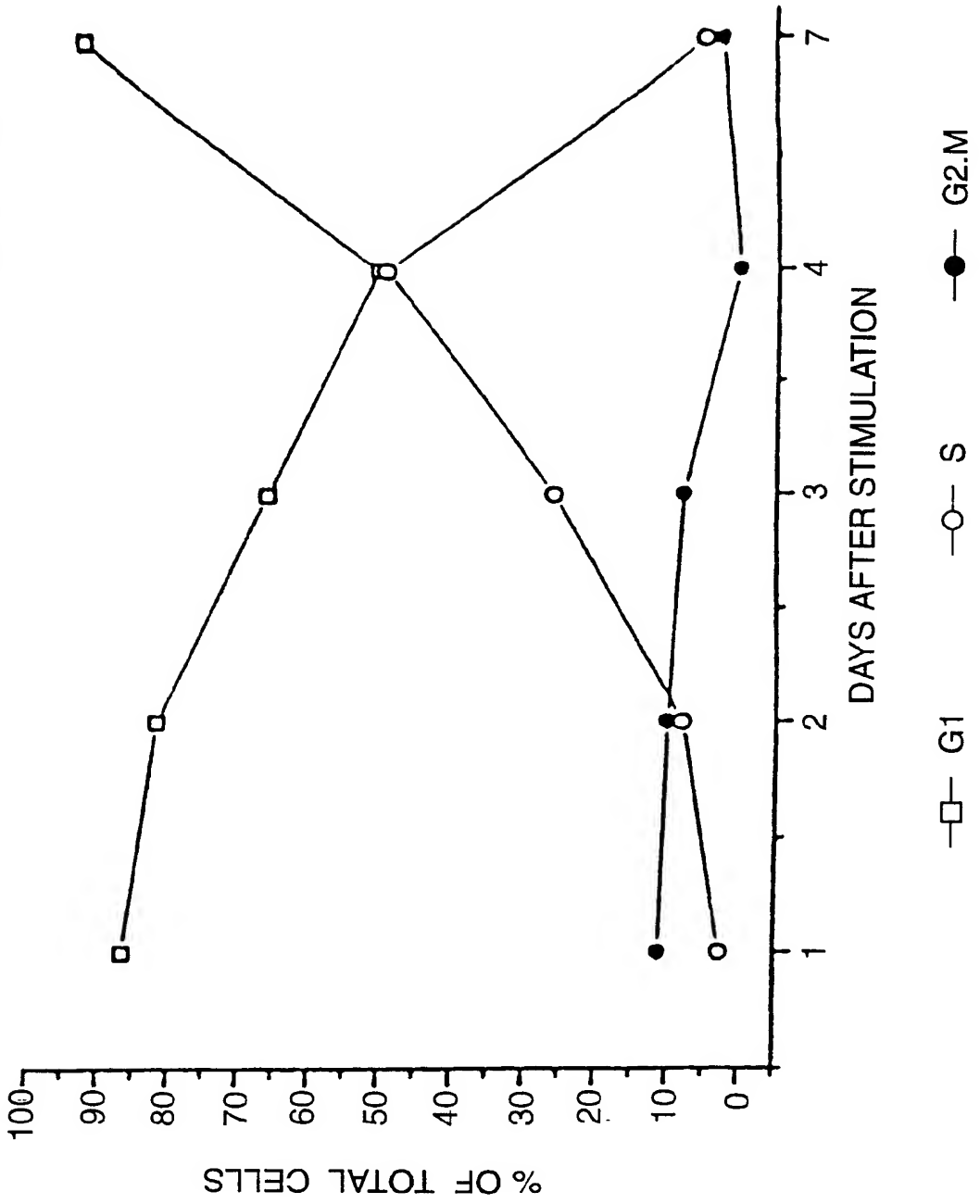


FIG. 4

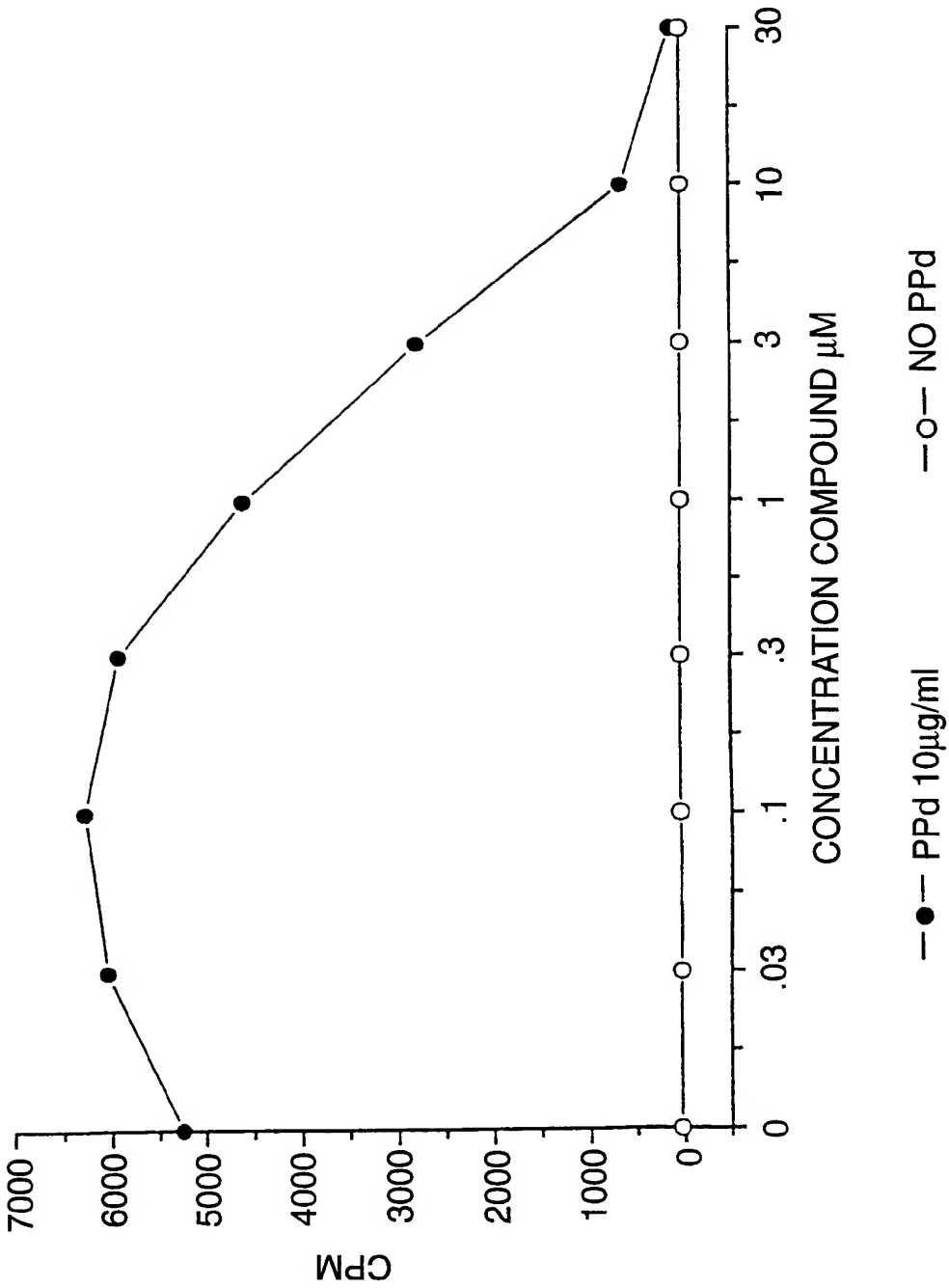

CPM
7000
6000
5000
4000
3000
2000
1000
0
0
.03
.1
.3
1
3
10
30
CONCENTRATION COMPOUND µM
—●— PPd 10µg/ml
—o— NO PPd

FIG. 5(a)

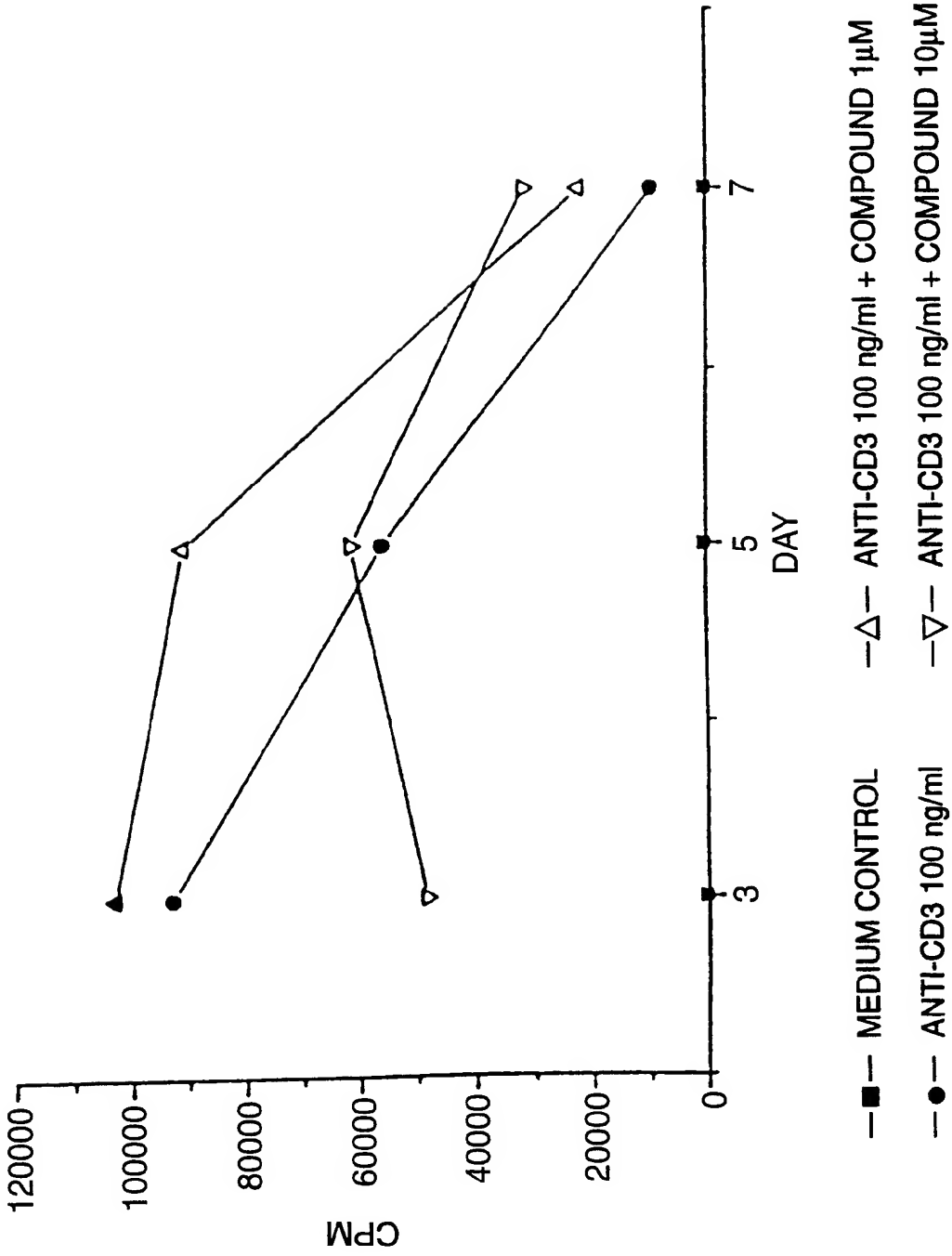
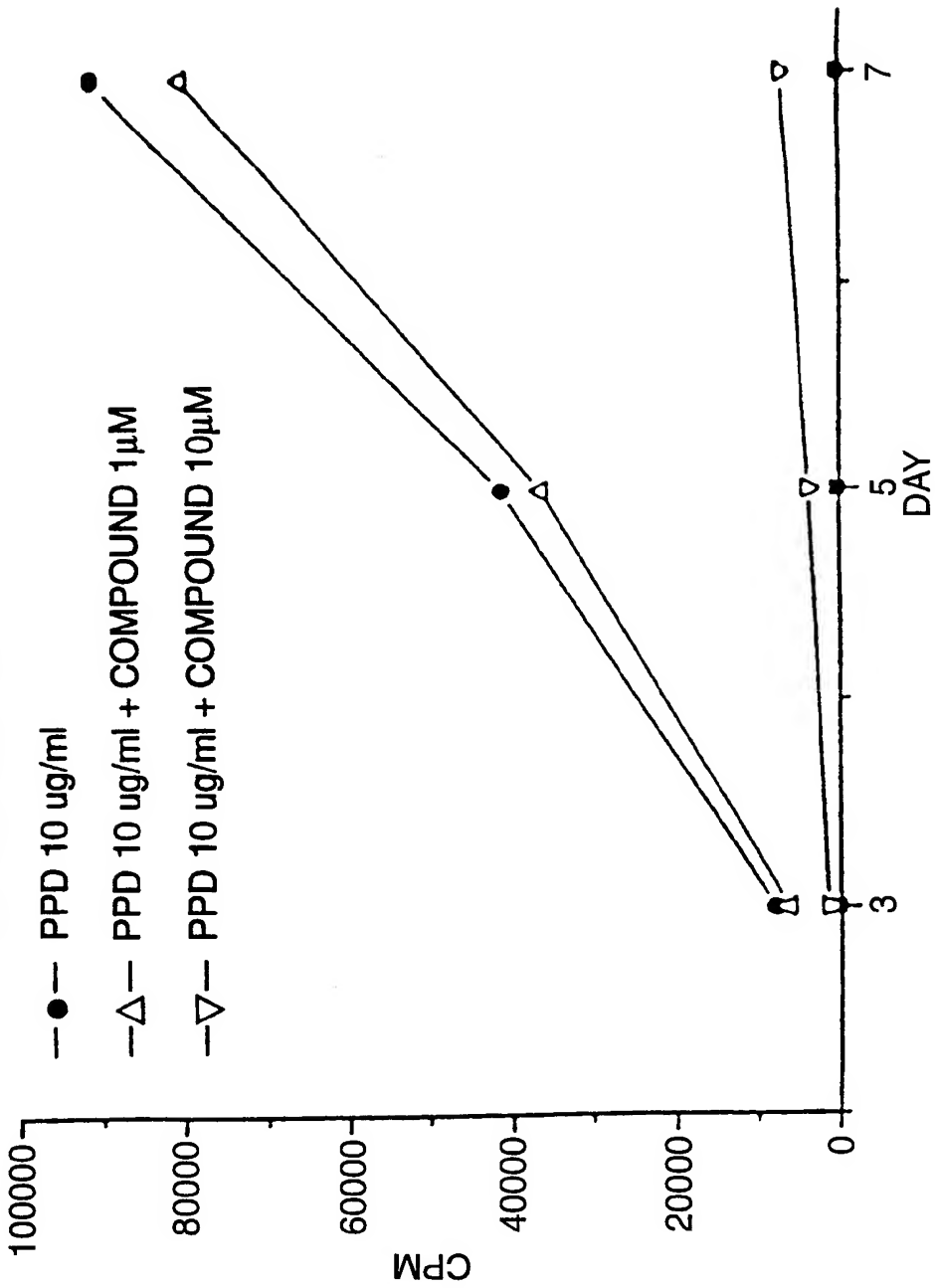

CPM
120000
100000
80000
60000
40000
20000
0
3
5
7
DAY
—■— MEDIUM CONTROL
—●— ANTI-CD3 100 ng/ml
—△— ANTI-CD3 100 ng/ml + COMPOUND 1μM
—▽— ANTI-CD3 100 ng/ml + COMPOUND 10μM

FIG. 5(b)


—■— MEDIUM CONTROL
—●— PPD 10 ug/ml
—△— PPD 10 ug/ml + COMPOUND 1μM
—▽— PPD 10 ug/ml + COMPOUND 10μM
CPM
100000
80000
60000
40000
20000
0
3
5
7
DAY

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/00580

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/44 A61K31/40 A61K31/415 A61K31/70 A61K31/445
A61K31/41 A61K31/42 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 94 02483 A (THE WELLCOME FOUNDATION LIMITED) 3 February 1994 (1994-02-03) cited in the application the whole document --- | 1-6, 13-22 |
| A | WO 95 21170 A (THE WELLCOME FOUNDATION LIMITED) 10 August 1995 (1995-08-10) cited in the application the whole document --- | 1-3,7,8, 13-22 |
| A | WO 95 21171 A (THE WELLCOME FOUNDATION LIMITED) 10 August 1995 (1995-08-10) cited in the application the whole document --- -/-- | 1-3,9, 10,13-22 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 26 July 1999 | 16/08/1999 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Mair, J |

1

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/00580

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 96 01827 A (THE WELLCOME FOUNDATION LIMITED) 25 January 1996 (1996-01-25) cited in the application the whole document | 1-3, 11-22 |

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/ 00580

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 18-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [X] Claims Nos.: 1-4, 7,9,11,13-22
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4, 7, 9, 11, 13-22

In view of the large number of compounds which are theoretically defined by the formulae of claims 1-4, 7, 9, 11 and 13-22 the search has had to be restricted on economic grounds to the specifically claimed compounds and the general concept underlying the application.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/00580

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
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| | | EP 0741729 A | 13-11-1996 |
| | | JP 9511491 T | 18-11-1997 |
| | | US 5852204 A | 22-12-1998 |
| WO 9521171 A | 10-08-1995 | AU 1542295 A | 21-08-1995 |
| | | EP 0807113 A | 19-11-1997 |
| WO 9601827 A | 25-01-1996 | AU 2805295 A | 09-02-1996 |
| | | EP 0769012 A | 23-04-1997 |
| | | JP 10502374 T | 03-03-1998 |
| | | TR 960032 A | 21-06-1996 |
| | | US 5770598 A | 23-06-1998 |